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2-([1,2,4]triazolo[1,5-c]quinazoline-2-yl-)alkyl-(alkaryl-,aryl-)-amines and their derivatives. The synthesis of (3*H*-quinazoline-4-ylidene) hydrazides *N*-protected aminoacids, using a variety of amine-protecting approaches. Physical-chemical properties and biological activity of synthesized compounds (Message 2)

Yu. V. Martynenko, M. S. Kazunin, I. S. Nosulenko, G. G. Berest, S. I. Kovalenko, O. M. Kamyshnyi, N. M. Polishchuk

Zaporizhzhia State Medical University, Ukraine

The synthetic potential of (3*H*-quinazoline-4-ylidene)hydrazides of carboxylic acids is significant in the context of new s-triazoloquinazolines creation and the obtained data of biological activity is a valid reason for the development of new methods of their synthesis, using a variety of reage nts. The introduction of *N*-protected aminoacids moieties into 4-hydrazinoquinazoline molecule is an important aspect, which solves this problem and extends the limits of hydrazides usage. The above would allow to change physical-chemical and biological properties of the corresponding hydrazides and it opens new perspectives of their practical application and further chemical transformations.

The aim of the work is synthesis of unknown (3*H*-quinazoline-4-ylidene)hydrazides of *N*-protected aminoacids, using various approaches of the amino group protection, research of structure features and finding effective biologically active substances with antimicrobial and antiradical activities among them.

Materials and methods. The individuality and structure of synthesized compounds was proved by elemental analysis, chromatomass- and 1H NMR spectra. In vitro research of antiradical activity was based on the interaction of synthesized compounds with 2,2-diphenyl-1-picrylhydrazyl (DPPH). The study of microbiological activity was conducted by serial dilution method on Mueller–Hinton broth on following strains of microorganisms and fungi: St. aureus ATCC 25923, E. coli ATCC 25922, P. aeruginosa ATCC 27853, C. albicans ATCC 885653.

Conclusions. A synthetic method for (3*H*-quinazoline-4-ylidene)hydrazides *N*-protected aminoacids, which was based on interaction of 4-hydrazinoquinazoline with "activated" *N*-protected aminoacids was elaborated. It was found, that benzoyl- and Boc-aminoacids were the most reliable substrates for the synthesis of the corresponding hydrazides. A detailed analysis of 1H NMR spectra allowed the unambiguous establishing of peculiar to (3*H*-quinazoline-4-ylidene)hydrazides *N*-protected aminoacids amid-imide tautomerism in DMSO solutions, due to the presence of hydrazide and amide groups. The microbiological screenings showed that hydrazides exhibited moderate antimicrobial activity against P. aeruginosa (MIC 50–100 μg/ml and MBC 100 μg/ml) and fungal activity against C. albicans (MIC 50 μg/ml, MBC 50–100 μg/ml). In addition, the synthesized compounds exhibited high antiradical activity, which indicated their prospects for further researches on other types of biological activity.

Key words: *N*-protected aminoacids, carbonyldiimidazoles synthesis, (3*H*-quinazoline-4-ylidene) hydrazides, physical-chemical properties, spectral features, biological activity.

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E-mail: martynenkou20@gmail.com

2-([1,2,4]тріазоло[1,5-c]хіназолін-2-іл-)алкіл-(алкарил-,арил-)-аміни та їхні похідні. Синтез (3*H*-хіназолін-4-іліден)гідразидів ациламінокислот із використанням різноманітних підходів захисту аміногрупи. Фізико-хімічні властивості та біологічна активність синтезованих сполук (Повідомлення 2)

Ю. В. Мартиненко, М. С. Казунін, І. С. Носуленко, Г. Г. Берест, С. І. Коваленко, О. М. Камишний, Н. М. Поліщук

Синтетичний потенціал (3*H*-хіназолін-4-іліден)гідразидів карбонових кислот є значущим у контексті створення на їх основі нових *s*-тріазолохіназолінів, а дані щодо біологічної активності є підставою для розробки нових методів їх побудови з використанням різноманітних реагентів. Важливим аспектом, що вирішує цю проблему та розширює межі застосування гідразидів, є введення залишків *N*-захищених амінокислот у молекулу 4-гідразинохіназоліну. Це дасть змогу цілеспрямовано змінити фізико-хімічні та біологічні властивості відповідних гідразидів і відкрити нові перспективи їх практичного застосування та наступних хімічних перетворень.

Мета роботи – синтез невідомих (3*H*-хіназолін-4-іліден)гідразидів *N*-захищених амінокислот із використанням різних підходів щодо захисту аміногрупи, вивчення особливостей їхньої будови та пошук серед них ефективних біологічно активних речовин із протимікробною та антирадикальною дією.

Матеріали та методи. Індивідуальність і будова синтезованих сполук доведена елементним аналізом, хромато-мас-та ^{1}H ЯМР-спектрами. Дослідження антирадикальної активності *in vitro* базується на взаємодії синтезованих сполук з 2,2-дифеніл-1-пікрилгідразилом (DPPH). Мікробіологічну активність вивчили методом серійних розведень на середовищі Мюллера–Хінтона на стандартних штамах мікроорганізмів і грибів: *St. aureus* ATCC 25923, *E. coli* ATCC 25922, *P. aeruginosa* ATCC 27853, *C. albicans* ATCC 885653.

Висновки. Уперше розроблений препаративний метод синтезу (3*H*-хіназолін-4-іліден)гідразидів *N*-захищених амінокислот як результат взаємодії 4-гідразинохіназоліну та «активованих» *N*-захищених амінокислот із використанням різноманітних підходів захисту аміногрупи. Встановили, що найбільш надійними субстратами для синтезу відповідних

Ключові слова: *N*-захищені амінокислоти, карбонілдіімідазольний синтез, (3*H*-хіназолін-4-іліден)гідразиди, фізико-хімічні властивості, спектральні особливості, біологічна активність.

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гідразидів є бензоїл- і Boc-амінокислоти. Детальний аналіз ^{1}H ЯМР-спектрів дав змогу однозначно встановити, що для (3*H*-хіназолін-4-іліден)гідразидів *N*-захищених амінокислот у розчинах ДМСО характерна амід-імідольна таутомерія шляхом наявності гідразидної та амідної груп. Мікробіологічний скринінг показав, що гідразиди виявляють помірну протимікробну активність щодо *P. aeruginosa* (MIC 50–100 мкг/мл і MBC 100 мкг/мл) і фунгіцидну активність щодо *C. albicans* (MIC 50 мкг/мл, MFC 50–100 мкг/мл). Крім того, синтезовані сполуки мають високу антирадикальну дію, що вказує на їхню перспективність для наступних досліджень на інші види біологічної активності.

Ключевые слова: *N*-защищенные аминокислоты, карбонилдиимидазольный синтез, (3*H*-хиназолин-4-илиден) гидразиды, физико-химические свойства, спектральные особенности, биологическая активность.

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2-([1,2,4]триазоло[1,5-*c*]хиназолин-2-ил)алкил-(алкарил-,арил-)амины и их производные. Синтез (3*H*-хиназолин-4-илиден)гидразидов ациламинокислот с использованием различных подходов защиты аминогруппы. Физико-химические свойства и биологическая активность синтезированных соединений (Сообщение 2)

Ю. В. Мартыненко, М. С. Казунин, И. С. Носуленко, Г. Г. Берест, С. И. Коваленко, А. Н. Камышный, Н. М. Полищук

Синтетический потенциал (3*H*-хиназолин-4-илиден)гидразидов карбоновых кислот имеет важное значение в контексте создания на их основе новых s-триазолохиназолинов, а данные, касающиеся биологической активности, являются основой для разработки новых методов их формирования с помощью различных реагентов. Важным аспектом, который решает эту проблему и расширяет пределы применения гидразидов, является введение «активированных» *N*-защищенных аминокислот в молекулу 4-гидразинохиназолина. Это позволит целенаправленно изменять физико-химические и биологические свойства соответствующих гидразидов и открывает новые перспективы для их практического применения и последующих химических превращений.

Цель работы – синтез неизвестных (3*H*-хиназолин-4-илиден)гидразидов *N*-защищенных аминокислот с использованием различных подходов защиты аминогруппы, изучение особенностей их структуры и поиск среди них эффективных биологически активных веществ с антимикробным и антирадикальным действием.

Материалы и методы. Индивидуальность и структура синтезированных соединений доказана элементным анализом, хромато-масс- и ^{1}H ЯМР-спектрами. Изучение антирадикальной активности синтезированных веществ проведено *in vitro* с использованием 2,2-дифенил-1-пикрилгидразила (DPPH). Изучение противомикробной активности проводили методом серийных разведений на среде Мюллера–Хинтона на стандартных штаммах микроорганизмов и грибов: *St. aureus* ATCC 25923, *E. coli* ATCC 25922, *P. aeruginosa* ATCC 27853, *C. albicans* ATCC 885653.

Выводы. Впервые разработан препаративный метод синтеза (3*H*-хиназолин-4-илиден)гидразидов *N*-защищенных аминокислот как результат взаимодействия 4-гидразинохиназолина и «активированных» *N*-защищенных аминокислот с использованием различных подходов к защите аминогруппы. Установлено, что наиболее надежными субстратами для синтеза соответствующих гидразидов оказались бензоил- и Boc-аминокислоты. Детальный анализ ^{1}H ЯМР-спектров позволил однозначно установить, что для (3*H*-хиназолин-4-илиден)гидразидов *N*-защищенных аминокислот в растворах ДМСО характерна амид-имидольная таутомерия вследствие наличия гидразидной и амидной групп. Микробиологический скрининг показал, что гидразиды проявляют умеренную антимикробную активность по отношению к *P. aeruginosa* (MIC 50–100 мкг/мл и MBC 100 мкг/мл) и фунгицидную активность по отношению к *C. albicans* (MIC 50 мкг/мл, MFC 50–100 мкг/мл). Кроме того, синтезированные вещества проявляют высокую антирадикальную активность, что указывает на их перспективность для изучения других видов биологической активности.

Introduction

Methods of (3*H*-quinazoline-4-ylidene)hydrazides synthesis in the context of functionalization and new condensed heterocycles obtaining on their basis remain insufficiently studied despite their significant synthetic potential [1–5]. Moreover, the data obtained over the last decade as for their biological activity and the "structure-activity relationship", without any doubt is a valid reason for the development of new methods of their synthesis using various reagents [4–6]. (3*H*-Quinazoline-4-ylidene)hydrazides of (1,3-dioxo-1,3-dihydro-2*H*-isoindole-2-yl)alkyl(alkaryl-,aryl-)carboxylic acids were also of some interest in this regard. They were synthesized by the "carbonyldiimidazole method", using protected by the phthalic residue [7] aminoacids. Mentioned above hydrazides proved the effectiveness as synthons in the synthesis of 2-([1,2,4]triazolo[1,5-*c*]quinazoline-2-yl)-alkyl-(alkaryl-, aryl)-isoindole-1,3(2*H*)-diones. However, the insignificant solubility of the last in polar solvents limits the routes of their administration during the pharmacological screening and their further modification, in particular, the removal of phthalic protection. A variety of approaches of the amino-group protection using acylating reagents is a positive factor, which can solve this problem and extend the scope of aminocarboxylic acids application. The introduction of *N*-protected aminoacids to 4-hydrazinoquinazoline molecule allows the purposeful modification of their physical, chemical and biological properties directly and it opens new perspectives for their application and subsequent chemical transformations.

The aim

Thus, the aim of this work is a synthesis of unknown (3*H*-quinazoline-4-ylidene)hydrazides *N*-protected aminoacids, using various approaches of the amino group protection, the research of their structure features and search of the effective biologically active substances as potential therapeutic agents.

Materials and methods

Experimental chemical part. Melting points were determined in open capillary tubes in a "Stuart SMP30" apparatus and were uncorrected. The elemental analyses (C, H, N) were

performed using the "ELEMENTAR vario EL cube" analyzer. ^{1}H NMR spectra (400 MHz) were recorded at "Varian-Mercury 400" spectrometer with $SiMe_4$ as internal standard in DMSO-d_6 solution. LC/MS spectra were recorded using chromatography/mass spectrometric system, which consists of high-performed liquid chromatograph "Agilent 1100 Series" equipped with diode-matrix and mass-selective detector "Agilent LC/MSD SL" (atmospheric pressure chemical ionization – 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 to the search of potential biologically active substances, using reagents of companies: "Sigma-Aldrich" (Missouri, USA) and "Enamine" (Kyiv, Ukraine).

N-Protected aminoacids (1.1a–1.20a) and 4-hydrazinoquinazoline (2.1) were synthesized according to the known methods a, b, c, d and their constants correspond to the literature [8, 9].

2.2. The general procedure for the synthesis of (3H-quinazoline-4-ylidene)hydrazides N-protected aminoacids (3.1–3.20). 1.62 g (0.01 M) of *N,N'*-carbonyldiimidazole was added to a suspension of 0.01 M of the corresponding acylaminoacid *(1.1a–1.10a)* in 30 ml of dioxane. The mixture was kept at temperature 60–70 °C for 50–60 minutes until the carbon dioxide was completely released. After addition of 1.6 g (0.01 M) 4-hydrazinoquinazoline (2.1) the mixture was kept at room temperature overnight or at 80 °C for 1.5 hour. If the reaction mixture was a solution, dioxane was distilled off. The water was added and the mixture was neutralized by 0.1 M of hydrochloric acid to pH 6–7. The solid product was filtered in the case of residue formation. If it was necessary, compounds were crystallized.

N-(2-Oxo-2-(2-(quinazoline-4(3H)-ylidene)hydrazinyl) ethyl)acetamide (3.1). Yield: 83.9 %; M.p. 200-202 °C; ^{1}H NMR, δ, ppm (*J*, Hz): 9.64 (brs, 1H, =NN*H*CO-), 8.27-8.18 and 7.77-7.71 (brt, 1H, -N*H*CO-), 8.06/7.90 (d, *J* = 7.1/7.8 Hz, 1H, H-5), 7.98/7.79 (s, 1H, H-2), 7.43-7.12 (m, 3H, H-6,7,8), 4.23/3.81 (d, *J* = 5.3/5.6 Hz, 2H, -CH_2-), 1.92/1.86 (s, 3H, -CH_3); LC/MS, *m/z* = 260 [M+1], 261 [M+2]; Anal. Calcd for $C_{12}H_{13}N_5O_2$: C, 55.59; H, 5.05; N, 27.01; Found: C, 55.64; H, 5.12; N, 27.07.

N-(4-(2-(Quinazoline-4(3H)-ylidene)hydrazine-1-carbonyl)benzyl)acetamide (3.2). Yield: 77.7 %; M.p. 244-246 °C; ^{1}H NMR, δ, ppm (*J*, Hz): 11.18 (s, 1H, 3-N*H*), 9.93 (brs, 1H, =NNHCO-), 8.30 (t, 1H, -N*H*CO-), 8.16 (d, *J* = 7.5 Hz, 1H, H-5), 8.03 (s, 1H, H-2), 7.84 (d, *J* = 7.7 Hz, 2H, Ph H-2,6), 7.42 – 7.25 (m, 4H, H-6, 8, Ph H-3,5), 4.32 (d, *J* = 5.5 Hz, 2H, -CH_2-), 1.90 (s, 3H, -CH_3); LC-MS, *m/z* = 336 [M+1], 337 [M+2]; Anal. Calcd for $C_{18}H_{17}N_5O_2$: C, 64.47; H, 5.11; N, 20.88; Found: C, 64.52; H, 5.17; N, 20.92.

(N-(4-(2-(Quinazoline-4(3H)-ylidene)hydrazine-1-carbonyl)phenyl)acetamide (3.3). Yield: 71.3 %; M.p. 256-258 °C; ^{1}H NMR, δ, ppm (*J*, Hz): 10.34 (brs, 1H, =NN*H*CO-), 9.99 (brs, 1H, -N*H*CO-), 8.54 (m, 1H, H-5, H-2), 8.20 (m, H-2, Ph H-2,6), 7.98-7.90 (m, 2H, H-7,8), 7.77-7.45 (m, 4H, H-6, Ph H-3,5), 2.10 (s, 3H, CH_3); LC/MS, *m/z* = 322 [M+1], 323 [M+2]; Anal. Calcd for $C_{17}H_{15}N_5O_2$: C, 63.54; H, 4.71; N, 21.79; Found: C, 63.62; H, 4.77; N, 21.83.

N-(2-Oxo-2-(2-(quinazoline-4(3H)-ylidene)hydrazinyl) ethyl)benzamide (3.4). Yield: 85.9 %; M.p. 193-194 °C; ^{1}H NMR, δ, ppm (*J*, Hz): 11.71 (brs, 1H, 3-N*H*), 10.48/10.38 (brs, 1H, =NN*H*CO-), 8.89/8.33 (br.s, 1H, -N*H*CO-), 8.20-7.70 (m, 4H, H-2,5, Ph H-2,6) 7.70-6.42 (m, 6H, H-6,7,8, Ph H-3,4,5), 4.45/4.06 (d, *J* = 5.4 Hz, 2H, CH_2); LC-MS, *m/z* = 322 [M+1], 323 [M+2]; Anal. Calcd for $C_{17}H_{15}N_5O_2$: C, 63.54; H, 4.71; N, 21.79; Found: C, 63.57; H, 4.78; N, 21.84.

N-(1-Oxo-1-(2-(quinazoline-4(3H)-ylidene)hydrazinyl) propan-2-yl)benzamide (3.5). Yield: 91.1 %; M.p. 127-129 °C; ^{1}H NMR, δ, ppm (*J*, Hz): 14.10 (brs, 1H, 3-N*H*), 11.21 (brs, 1H, =NN*H*CO-), 8.86 (brs, 1H, -N*H*CO-), 8.42 (m, 2H, Ph H-2,6), 7.98-7.84 (m, 1H, H-5), 7.75 (s, 1H, H-2), 7.63-7.24 (m, 3H, Ph H-3,4,5), 7.08 (m, 1H, H-7), 6.80 (m, 1H, H-6), 6.61 (m, 1H, H-8), 4.52-4.40 (m, 1H, -C*H*(CH_3)), 1.45 (s, 3H, -CH_3); LC/MS, *m/z* = 336 [M+1], 337 [M+2]; Anal. Calcd for $C_{18}H_{17}N_5O_2$: C, 64.47; H, 5.11; N, 20.88; Found: C, 64.53; H, 5.18; N, 20.94.

N-(3-Oxo-3-(2-(quinazoline-4(3H)-ylidene)hydrazinyl) propyl)benzamide (3.6). Yield: 78.9 %; M.p. 142-144 °C; ^{1}H NMR, δ, ppm (*J*, Hz): 11.46 (s, 1H, 3-N*H*), 10.08/9.56 (brs, 1H, =NN*H*CO-), 8.48-8.38/8.33-8.23 (m, 1H, -N*H*CO-), 7.91 (d, *J* = 7.6 Hz, 1H, H-5), 7.88-7.81 (m, 2H, Ph H-2,6), 7.75 (s, 1H, H-2), 7.47-7.30 (m, 4H, H-9, Ph H-3,4,5), 7.19 (s, 1H, H-10), 7.12 (s, 1H, H-8), 3.74-3.44 (m, 2H, -CH_2C$\underline{H}_2$NH-), 2.62-2.55 (m, 2H, -C$\underline{H}_2$$CH_2$NH-); LC/MS, *m/z* = 336 [M+1], 337 [M+2]; Anal. Calcd for $C_{18}H_{17}N_5O_2$: C, 64.47; H, 5.11; N, 20.88; Found: C, 64.58; H, 5.20; N, 20.96.

N-(3-Methyl-1-oxo-1-(2-(quinazoline-4(3H)-ylidene) hydrazinyl)butan-2-yl)benzamide (3.7). Yield: 99.5 %; M.p. 136-138 °C; ^{1}H NMR, δ, ppm (*J*, Hz): 11.61 (s, 1H, 3-N*H*), 10.35/9.72 (brs, 1H, =NN*H*CO-), 8.43 (m, 1H, -N*H*CO-), 7.92 (d, *J* = 6.8 Hz, 2H, Ph H-2,6), 7.87/7.76 (d, *J* = 6.7 Hz, 1H, H-5), 7.78 (s, 1H, H-2), 7.53-7.35 (m, 4H, H-7, Ph H-3,4,5), 7.26 (t, 1H, H-6), 7.17 (d, 1H, H-8), 5.56-5.35/4.38-4.32 (m, 1H, C$\underline{H}$CH(CH_3)$_2$), 2.46-2.37/2.36-2.23 (m, 1H, CH-C$\underline{H}$(CH_3)$_2$), 1.04 (m, 6H, CHCH(C$\underline{H}_3$)$_2$); LC/MS, *m/z* = 360 [M+1], 361 [M+2]; Anal. Calcd for $C_{20}H_{21}N_5O_2$: C, 66.10; H, 5.82; N, 19.27; Found: C, 60.13; H, 5.89; N, 19.34.

N-(4-Methyl-1-oxo-1-(2-(quinazoline-4(3H)-ylidene) hydrazinyl)pentan-2-yl)benzamide (3.8). Yield: 51.3 %; M.p. 101-103 °C; ^{1}H NMR, δ, ppm (*J*, Hz): 11.49 (s, 1H, 3-N*H*), 10.36/9.58 (brs, 1H, =NN*H*CO-), 8.74-8.47/8.21-8.10 (m, 1H, -N*H*CO-), 8.01-7.87 (m, 3H, H-5, Ph H-2,6), 7.78 (s, 1H, H-2), 7.56-7.35 (m, 4H, H-7, Ph H-3,4,5), 7.32-6.90 (m, 2H, H-6,8), 5.52/4.64 (t, 1H, C$\underline{H}$$CH_2$CH($CH_3$)$_2$), 2.01-1.51 (m, 2H, CHC$\underline{H}_2$CH($CH_3$)$_2$), 1.29-1.05 (m, 1H, CHC$H_2C\underline{H}$($CH_3$)$_2$), 1.07-0.84 (m, 6H, CHC$H_2$CH(C$\underline{H}_3$)$_2$); LC/MS, *m/z* = 378 [M+1], 379 [M+3]; Anal. Calcd for $C_{21}H_{23}N_5O_2$: C, 66.83; H, 6.14; N, 18.55; Found: C, 66.80; H, 6.09; N, 18.44.

N-(4-(Methylthio)-1-oxo-1-(2-(quinazoline-4(3H)-ylidene)hydrazinyl)butan-2-yl)benzamide (3.9). Yield: 85.7 %; M.p. 226-228 °C; ^{1}H NMR, δ, ppm (*J*, Hz): 11.63 (s, 1H, 3-N*H*), 10.44/9.67 (brs, 1H, =NN*H*CO-), 8.67/8.19 (d, *J* = 7.6/8.1 Hz, 1H, -N*H*CO-), 8.07 (d, *J* = 7.5 Hz, 1H, H-5), 8.03-7.88 (m, 2H, Ph H-2,6), 7.79 (s, 1H, H-2), 7.59-7.10 (m, 6H, H-6,7,8, Ph H-3,4,5), 5.58-5.43 (m, 1H, -C$\underline{H}$$CH_2$$CH_2SCH_3$), 4.80-4.55/2.68-2.54 (m, 2H, -CHC$\underline{H}_2$$CH_2SCH_3$), 2.13-1.95 (m, 5H, -CHCH_2C$\underline{H}_2$S$C\underline{H}_3$); LC/MS, *m/z* = 396 [M+1], 398 [M+3]; Anal. Calcd for $C_{20}H_{21}N_5O_2S$: C, 60.74; H, 5.35; N, 17.71; Found: C, 60.83; H, 5.38; N, 17.76.

N-(1-Oxo-3-phenyl-1-(2-(quinazoline-4(3H)-ylidene) hydrazinyl)propan-2-yl)benzamide (3.10). Yield: 86.2 %; M.p. 144-146 °C; ^{1}H NMR, δ, ppm (*J*, Hz): 12.51 (brs, 1H,

=NN*H*CO-), 8.67 (m, 1H, -N*H*CO-), 8.42 (d, *J* = 7.6 Hz, 1H, H-5), 7.84-7.69 (m, 3H, H-2, Ph H-2,6), 7.55-7.10 (m, 11H, H-6,7,8, Ph H-3,4,5, Bz H-2,3,4,5,6), 4.96-4.03 (m, 1H, C*H*CH_2), 3.39-2.82 (m, 2H, CHC*H*$_2$); LC/MS, *m/z* = 412 [M+1], 413 [M+2]; Anal. Calcd for $C_{24}H_{21}N_5O_2$: C, 70.06; H, 5.14; N, 17.02; Found: C,70.15; H, 5.20; N, 17.06.

N-(4-(2-(Quinazoline-4(3H)-ylidene)hydrazine-1-carbonyl)benzyl)benzamide (3.11). Yield: 98.7 %; M.p. 215-217 °C; ^{1}H NMR, δ, ppm (*J*, Hz): 11.08 (brs, 1H, =NN*H*CO-), 9.05 (t, 1H, -N*H*CO-), 8.62 (s, 1H, H-2), 8.53 (d, *J* = 8.3 Hz, 1H, H-5), 7.98-7.77 (m, 6H, H-7,8, Ph H-2,6, Bz H-2,6), 7.71-7.57 (m, 1H, H-6), 7.56-7.29 (m, 5H, Ph H-3,5, Bz H-3,4,5), 4.57 (d, *J* = 5.2 Hz, 2H, -CH_2-); LC/MS, *m/z* = 398 [M+1], 399 [M+2]; Anal. Calcd for $C_{23}H_{19}N_5O_2$: C, 69.51; H, 4.82; N, 17.62; Found: C, 69.47; H, 4.79; N, 17.56.

N-(3-(1H-Indole-3-yl)-1-oxo-1-(2-(quinazoline-4(3H)-ylidene)hydrazinyl)propan-2-yl)benzamide (3.12). Yield: 48.7 %; M.p. 164-166 °C; ^{1}H NMR, δ, ppm (*J*, Hz): 10.66 (brs, 1H, =NN*H*CO-), 10.62 (s, 1H, indole H-2), 10.47/9.81 (s, 1H, -N*H*CO-), 8.86-6.50 (m, 14H, H-2,5,6,7,8, Ph H-2,3,4,5,6, indole H-4,5,6,7), 5.00-4.87/4.87-4.62 (m, 1H, C*H*CH_2), 3.54-3.14 (m, 2H, CHC*H*$_2$); LC/MS, *m/z* = 451 [M+1], 452 [M+2], 453 [M+3]; Anal. Calcd for $C_{26}H_{22}N_6O_2$: C, 69.32; H, 5.35; N, 18.57; Found: C, 69.36; H, 5.39; N, 18.58.

N-(4-(2-(Quinazoline-4(3H)-ylidene)hydrazine-1-carbonyl)phenyl)benzamide (3.13). Yield: 97.2 %; M.p. 294-296 °C; ^{1}H NMR, δ, ppm (*J*, Hz): 10.80 (brs, 1H, =NN*H*CO-), 10.39 (s, 1H, -N*H*CO-), 8.41-8.21 (m, 2H, H-2, 5), 8.02 (d, *J* = 7.0 Hz, 2H, Bz H-2,6), 7.98-7.90 (m, 4H, H-7,8, Ph H-2,6), 7.77-7.45 (m, 6H, H-6, Bz H-3,4,5, Ph H-3,5); LC/MS, *m/z* = 384 [M+1], 385 [M+2]; Anal. Calcd for $C_{22}H_{17}N_5O_2$: C, 68.92; H, 4.47; N, 18.27; Found: C, 69.01; H, 4.56; N, 18.34.

Tert-butyl (2-oxo-2-(2-(quinazoline-4(3H)-ylidene) hydrazinyl)ethyl)carbamate (3.14). Yield: 69.4 %; M.p. 206-207 °C; ^{1}H NMR, δ, ppm (*J*, Hz): 11.43 (s, 1H, 3-N*H*), 10.31/9.59 (brs, 1H, =NN*H*CO-), 7.99/7.88 (d, *J* = 7.7 Hz, 1H, H-5), 7.76 (s, 1H, H-2), 7.38 (t, 1H, H-7), 7.20 (t, 1H, H-6), 7.11 (d, *J* = 7.9 Hz, 1H, H-8), 6.20/6.04 (t, *J* = 4.7 Hz, 1H, -N*H*Boc), 4.13/3.67 (d, *J* = 4.6 Hz, 2H, -CH_2-), 1.43 (s, 9H, $(CH_3)_3$C-); LC/MS, *m/z* = 318 [M+1], 319 [M+2]; Anal. Calcd for $C_{15}H_{19}N_5O_3$: C, 56,77; H, 6.03; N, 22.07; Found: C, 56.84; H, 6.06; N, 22.12.

Tert-butyl (3-methyl-1-oxo-1-(2-(quinazoline-4(3H)-ylidene)hydrazinyl)butan-2-yl)carbamate (3.15). Yield: 96.0 %; M.p. 154-156 °C; ^{1}H NMR, δ, ppm (*J*, Hz): 11.57 (s, 1H, 3-N*H*), 10.20/9.61 (brs, 1H, =NN*H*CO-), 8.04/7.87 (d, *J* = 8.2 Hz, 1H, H-5), 7.92/7.77 (s, 1H, H-2), 7.87 (d, *J* = 8.2 Hz, 3H), 7.52-7.43/7.42-7.34 (m, 1H, H-7), 7.32-7.25/7.25-7.19 (m, 1H, H-6), 7.32-7.25/7.14 (d, *J* = 7.6 Hz, 1H, H-8), 6.52 (d, *J* = 4.8 Hz, 1H, -N*H*Boc), 5.92-5.54 (m, 1H, C*H*-CH$(CH_3)_2$) and 4.90 (d, *J* = 6.5 Hz, 1H, C*H*CH$(CH_3)_2$), 2.25-2.17/2.09 (m, 1H, CHC*H*$(CH_3)_2$), 1.60-1.23 (m, 9H, $(CH_3)_3$C), 1.09 – 0.64 (m, 6H, CHCH$(CH_3)_2$); LC/MS, *m/z* = 360 [M+1], 361 [M+2]; Anal. Calcd for $C_{18}H_{25}N_5O_3$: C, 60.15; H, 7.01; N, 19.47; Found: C, 60.23; H, 7.08; N, 19.54.

Tert-butyl (4-(methylthio)-1-oxo-1-(2-(quinazoline-4(3H)-ylidene)hydrazinyl)butan-2-yl)carbamate (3.16). Yield: 38.3 %; M.p. 134-136 °C; ^{1}H NMR, δ, ppm (*J*, Hz): 11.44 (s, 1H, 3-N*H*), 10.37/9.56 (brs, 1H, =NN*H*CO), 7.95 (d, *J* = 8.7 Hz, 1H, H-5), 7.77 (s, 1H, H-2), 7.38 (d, *J* = 7.4 Hz, 1H, H-7), 7.21 (t, *J* = 7.4 Hz, 1H, H-6), 7.12 (d, *J* = 7.3 Hz, 1H, H-8), 6.33 (d, *J* = 8.1 Hz, 1H, -N*H*Boc), 5.22-4.85 (m, 1H, C*H*$CH_2CH_2SCH_3$), 4.32-3.88/2.65-2.51 (m, 2H, -CHC*H*$_2CH_2SCH_3$), 2.22-1.94 (m, 5H, -CHCH_2C*H*$_2$SC*H*$_3$), 1.53-1.26 (m, 9H, C*H*$_3$)$_3$C-); LC/MS, *m/z* = 392 [M+1], 394 [M+3]; Anal. Calcd for $C_{18}H_{25}N_5O_3S$: C, 55.22; H, 6.44; N, 17.89; Found: C, 55.31; H, 6.49; N, 17.93.

Tert-butyl (1-oxo-3-phenyl-1-(2-(quinazoline-4(3H)-ylidene)hydrazinyl)propan-2-yl)carbamate (3.17). Yield: 76.9 %; M.p. 157-159 °C; ^{1}H NMR, δ, ppm (*J*, Hz): 11.48 (s, 1H, 3-NH), 10.38/9.62 (brs, 1H, =NN*H*CO-), 7.98 (d, *J* = 7.1 Hz, 1H, H-5), 7.79 (s, 1H, H-2), 7.40 (t, *J* = 7.1 Hz, 1H, H-6), 7.29-7.10 (m, 5H, Ph H-2, 3, 4, 5, 6), 6.99-6.45 (m, 2H, H-6,8), 6.24 (d, *J* = 8.1 Hz, 1H, -N*H*Boc), 5.34-5.01/4.50-3.95 (m, 1H, -C*H*CH_2Ph), 3.35-2.70 (m, 2H, -CHC*H*$_2$Ph), 1.36 (s, 9H, $(CH_3)_3$C-); LC/MS, *m/z* = 408 [M+1], 410 [M+3]; Anal. Calcd for $C_{22}H_{25}N_5O_3$: C, 64.85; H, 6.16; N, 17.19; Found: C, 64.91; H, 6.21; N, 17.26.

Tert-butyl (3-(1H-indole-3-yl)-1-oxo-1-(2-(quinazoline-4(3H)-ylidene)hydrazinyl)propan-2-yl)carbamate (3.18). Yield: 26.9 %; M.p. 163-165 °C; ^{1}H NMR, δ, ppm (*J*, Hz): 11.48 (s, 1H, 3-N*H*), 10.61/10.56 (brs, 1H, indole N*H*), 10.26/9.65 (brs, 1H, =NN*H*CO-), 7.95 (d, *J* = 8.1 Hz, 1H, H-5), 7.80 (s, 1H, H-2), 7.66-7.55 (m, 1H, indole H-4), 7.46-7.35 (m, 1H, H-7), 7.34-7.26 (m, 1H, indole H-7), 7.27-7.19 (m, 1H, H-6), 7.14 (d, *J* = 7.9 Hz, 1H, H-8), 7.10 (s, 1H, indole H-2), 7.06-6.87 (m, 2H, indole H-5,6), 6.17 (d, *J* = 8.4 Hz, 1H, -N*H*Boc), 5.25-5.12/4.45-4.01 (m, 1H, C*H*CH_2), 3.42-3.23 (m, 2H, CHC*H*$_2$), 1.40/1.38 (s, 9H, $(CH_3)_3$C-); LC/MS, *m/z* = 447 [M+1], 449 [M+3]; Anal. Calcd for $C_{24}H_{26}N_6O_3$: C, 64.56; H, 5.87; N, 18.82; Found: C, 64.62; H, 5.92; N, 18.86.

Tert-butyl (4-(2-(quinazoline-4(3H)-ylidene)hydrazine-1-carbonyl)benzyl)carbamate (3.19). Yield: 75.0 %; M.p. 240-242 °C; ^{1}H NMR, δ, ppm (*J*, Hz): 11.46 (s, 1H, 3-N*H*), 10.55 (brs, 1H, =NN*H*CO-), 8.20-8.11 (m, 3H, H-2, Ph H-2,6), 7.86-7.77 (m, 1H, H-5), 7.58-7.48 (m, 1H, H-7), 7.43-7.30 (m, 4H, H-6,8, Ph H-3,5), 7.18-7.05 (m, 1H, -N*H*Boc), 4.22 (d, *J* = 5.3 Hz, 2H, C*H*$_2$-), 1.44 (s, 9H, $(CH_3)_3$C-); LC/MS, *m/z* = 394 [M+1], 396 [M+3]; Anal. Calcd for $C_{21}H_{25}N_5O_3$: C, 64.11; H, 5.89; N, 17.80; Found: C, 64.17; H, 5.93; N, 17.87.

Tert-butyl (4-(2-(quinazoline-4(3H)-ylidene)hydrazine-1-carbonyl)phenyl)carbamate (3.20). Yield: 98.7 %; M.p. 173-175 °C; ^{1}H NMR, δ, ppm (*J*, Hz): ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.21 (brs, 1H, =NN*H*CO-), 8.20-8.11 (m, 3H, H-2, Ph H-2,6), 8.25 (m, 1H, H-5), 7.58-7.48 (m, 1H, H-7), 7.63-7.30 (m, 4H, H-6,8, Ph H-3,5), 7.55 (m, 1H, -N*H*Boc), 1.86 (s, 9H, $(CH_3)_3$C-); LC/MS, *m/z* = 380 [M+1], 381 [M+2]; Anal. Calcd for $C_{20}H_{21}N_5O_3$: C, 63.31; H, 5.58; N, 18.46; Found: C, 63.36; H, 5.64; N, 18.54.

The synthesized compounds 3.1–3.20 are yellow substances, soluble in DMF, DMSO, dioxane, alcohol, insoluble in water.

Antiradical activity. Research of antiradical activity *in vitro* was based on the interaction of synthesized compounds with 2,2-diphenyl-1-picrylhydrazyl (DPPH) [10,11]. DPPH is a stable free radical and its alcohol solutions are colored in intense purple color (λ_{max} = 517 nm). DPPH interacted with compounds that are able to bind with free radicals yields products, which are yellow colored and does not absorb the light at the specified above wavelengths.

Research methodology. 2 ml of 1 mM solution of

compound in DMSO was mixed with 2 ml of 0.1 mM DPPH methanol solution and it was incubated for 30 minutes at the temperature of 25 °C and optical density (A_d) was measured [10,11]. The optical density of 2 ml of 0.1 mM DPPH solution in 2 ml of methanol (A_{DPPH}) was determined simultaneously. Antiradical activity (ARA) was calculated by the next formula: ARA % = $(A_{DPPH}-A_d)/A_{DPPH} \times 100$ %. In the case of a negative meaning ARA in % was estimated like 0. Weighing reagents and synthesized compounds were conducted on electronic scales "ANG200C" and the optical density was measured by a spectrophotometer ULAB108UV.

Statistical data processing was carried out by using the standard package of statistical program analysis processing results, version Microsoft Office Excel 2003, Statistica® for Windows 6.0 (StatSoft Inc., № AXXR712D-833214FAN5). Parameters of arithmetic mean (M) and standard error and representativeness of the arithmetic mean (m) for each investigated compound were calculated. At the level of significance $P < 0.05$ the null hypotheses was rejected when the statistical hypotheses was checked.

Antimicrobial and antifungal activity. Sensitivity of microorganisms to the synthesized compounds was evaluated according to the described methods [12]. The assay was conducted on Mueller–Hinton broth by two-fold serial dilution of compound in 1 ml. After that 0.1 ml of microbial seeding (10^6 cells/ml) was added. Minimal inhibit concentration of compound was determined by the absence of visual growth in the test tube with the minimal concentration of substance, minimal bactericide/fungicide concentration was determined by absence of growth in broth after inoculation of microorganism from transparent test-tubes. DMSO was used as a solvent, initial solution concentration was 1 mg/ml. For preliminary screening the mentioned ahead standard test cultures were used: *St. aureus* ATCC 25923, *E. coli* ATCC 25922, *P. aeruginosa* ATCC 27853 and *C. albicans* ATCC 885-653. All test strains were received from bacteriological laboratory in Zaporizhzhya Regional Laboratory Center of State Sanitary and Epidemiological Service of Ukraine. Nitrofural and Ketoconazol were used as reference compounds with proved antibacterial/antifungal activity. Additional quality control of culture medium and solvents was conducted by commonly used methods [12].

Results and discussion

The protection of amino group in the corresponding aminoacids (1.1–1.10) was performed on the first stage, using various reagents (acetic anhydride, benzoylchloride, Boc_2O) [8] to continue our research dedicated to the synthesis of (3*H*-quinazoline-4-ylidene)hydrazides *N*-protected aminoacids as promising biologically active substances. Hydrazides 3.1–3.20 were obtained *via* interaction of generated *in situ* imidazolides of the *N*-protected aminoacids (1.1a–1.20a) with 4-hydrazinoquinazoline (2.1, *Scheme 1*). The most reliable substrates for the synthesis of 3.1–3.20 derivatives were benzoyl- and Boc-aminoacids, which unlike to acetylaminoacids during the process of the carboxyl group activation did not form side products as a result of intra- and intermolecular cyclization. The reaction proceeded regioselectively with high yields (LC/MS control) in case of these aminoacids usage. It is important to note, that the presence of an anhydrous solvent (dioxane) and the temperature conditions control (not above 80 °C) is obligatory for the occurrence of the indicated reaction. Abovementioned conditions prevented the subsequent cyclocondensation of compounds 3.1–3.20 and the formation of triazoloquinazolines as side-products.

Structure and individuality of compounds 3.1–3.20 were confirmed by data of chromato-mass-spectrometry and ^{1}H NMR spectroscopy. In chromato-mass spectra of the compounds 3.1–3.20 the signals of molecular ions

Scheme 1.

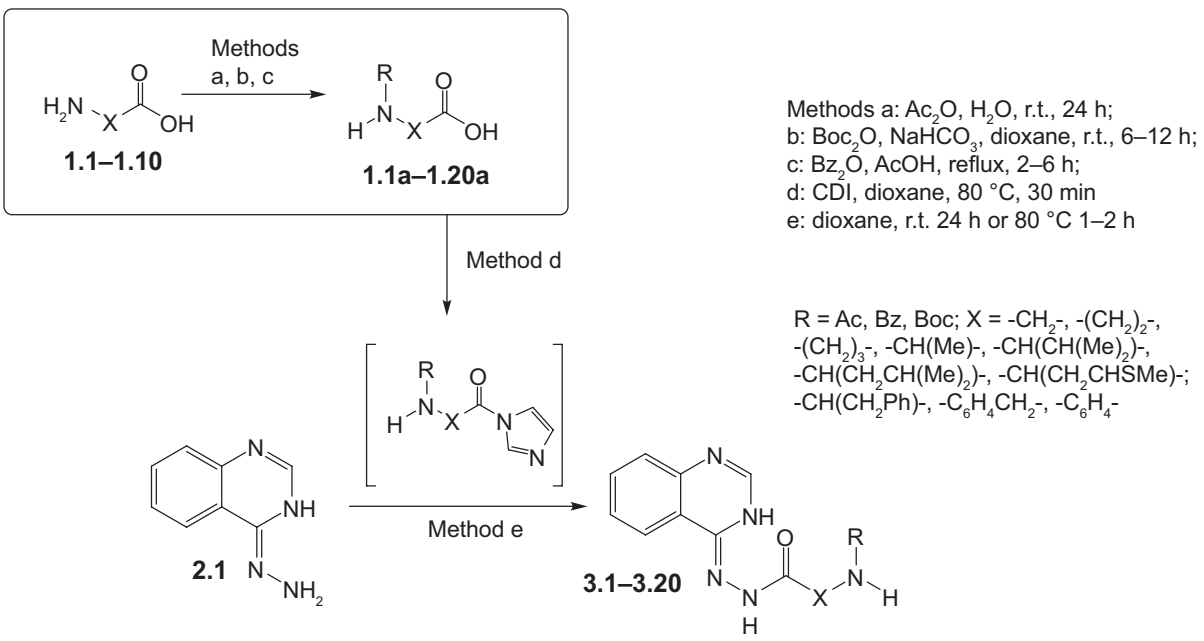

Table 1. Antimicrobial and antifungal activity data of the synthesized compounds, μg/ml*

Sub.[a]	E. coli		St. aureus		P. aeruginosa		C. albicans	
	MIC	MBC	MIC	MBC	MIC	MBC	MIC	MFC
3.1	100	200	100	200	50	100	50	100
3.3	100	200	100	200	50	100	50	100
3.4	100	200	100	200	50	100	50	100
3.6	100	200	100	200	50	100	50	100
3.7	100	200	100	200	50	100	50	50
3.8	100	200	100	200	100	200	50	50
3.9	100	200	100	200	50	100	50	100
3.10	100	200	100	200	50	100	50	100
3.11	100	200	100	200	50	100	50	100
3.12	100	200	100	200	100	200	50	100
3.13	100	200	100	200	100	200	50	100
3.14	100	200	100	200	50	100	50	100
3.16	100	200	100	200	50	100	50	50
3.17	100	200	100	200	50	100	50	100
3.18	100	200	100	200	100	100	50	100
3.19	100	200	100	200	50	100	50	100
Nitrofural	1.5	–	6.25	–	6.25	–	–	
Ketoconazole	–	–	–	–	–	–	25	50

MIC: minimal inhibitory concentration; **MBC**: minimal bactericidal concentration;
MFC: minimal fungicidal concentration.

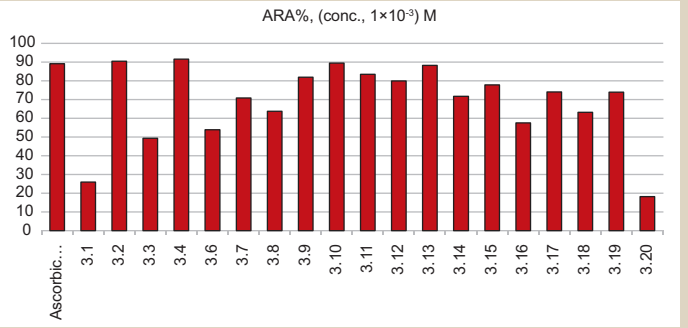

Fig. 1. Antiradical activity data of the synthesized compounds.

[M+1], [M+2] and [M+3] with *m/z* values that correspond to proposed structures were observed. Mentioned fact indicated the nucleophilic substitution reaction and the formation of the corresponding hydrazides. The ^{1}H NMR spectra of compounds 3.1–3.20 were characterized by the signals of hydrazide group and amide fragments *NH*-protons. Signals of hydrazide moiety *NH*-protons were observed as a broad singlet or doublets at the 11.08–9.55 ppm. Signals of amide group *NH*- protons depending on the magnetic environment resonated as triplets, broad triplets or singlets. In some cases, abovementioned protons were additionally doubled, what indicated the prototropic (amide-imide) tautomeric transformations in molecules of synthesized compounds. It is important, that the hydrazine-hydrazone tautomerism is not typical for the 4-hydrazinoquinazoline ring, that exists in the 4(3*H*)-form [7]. Abovementioned fact was proved by the signals in the low field (14.10–10.66 ppm), that associated with protons in position 3. Signals of protective groups protons were registered as three-proton singlet at the 2.10–1.86 ppm for compounds 3.1–3.3, multiplets of H-2,6 and H-3,4,5 in "aromatic area", which in some cases were overlapped with the signals of the quinazoline cycle or aromatic fragment in position 2 for 3.4–3.13 and a nine-proton singlets of *tert*-butyloxycarbonyl group at the 1.86–1.23 ppm for compounds 3.14–3.20. The signals of the quinazoline cycle protons were registered in the form of broad wide multiplets in the "aromatic" part of the spectrum together with benzoyl and phenyl groups and were less informative. However, signals of protons in postions 2 and 5 of quinazoline cycle were observed in relatively lower field as singlets at the 8.62-7.69 ppm and doublets at the 8.54–7.84 ppm, respectively.

The aromatic protons of the "linker" phenylene substituent (3.2, 3.3, 3.11, 3.13, 3.19, 3.20) were registered as A_2B_2-system formed by signals of H-2,6 protons as doublets and the signals of H-3,5 protons, that were overlapped with signals of H-5 and H-6 of quinazoline cycle. As for signals of the aliphatic groups protons in the ^{1}H NMR spectra of compounds 3.1–3.20, their multiplicity and chemical shift were determined by the magnetic environment. For example, the signals of methylene group protons of compounds 3.1, 3.2, 3.4, 3.11, 3.14 were characterized by doubled of doublets at the 4.57–3.67 ppm. Additional splitting was caused by the *NH*-group and the tautomeric transformations in the molecules. Elongation or branching of aliphatic residue (3.5–3.10, 3.15–3.18) led to more complex spectral patterns and signals appeared predominately as multiplets.

The study of antiradical activity of the synthesized compounds as one of the possible mechanisms of the pharmacological properties was conducted to evaluate promising areas of bioactivity screening. This decision was caused by the fact, that compounds with tautomeric transitions in molecules are characterized by this activity, but not enough explored [13–16]. The conducted studies confirmed this assumption. Indeed, compounds 3.1–3.20 exhibited high antiradical activity at a concentration of 10^{-3} M, which competed with the reference drug activity, namely Ascorbic acid (*Fig. 1*). It is important, that more expressed activity was characteristic for (3*H*-quinazoline-4-ylidene) hydrazides benzoylaminoacids (3.4–3.13), which inhibited the formation of free radicals at 54–92 %. This fact probably caused by higher acidic properties of the amide fragment in molecules of abovementioned compounds. In addition, this type of activity is characteristic not only for compounds 3.1–3.13, but also for insufficient known Boc-protected derivatives (3.14–3.20). Named compounds inhibited the radicals by 18–78 %.

Analysis of the obtained results of microbiological study showed, that synthesized compounds 3.1–3.20 revealed low activity against *E. coli* and *St. aureus* (MIC 100 μg/ml, MBC 200 μg/ml). However, they exhibited moderate antimicrobial activity against *P. aeruginosa* (MIC 50–100 μg/ml and MBC 100 μg/ml) and antifungal activity against *C. albicans* (MIC 50 μg/ml, MFC 50–100μg /ml). It is important, that antifungal activity of compounds 3.1–3.20 competed with the reference compound Ketoconazole.

So, conducted studies showed, that (3*H*-quinazoline-4-ylidene)hydrazides *N*-protected aminoacids (3.1–3.20) is the promising class of biologically active compounds and requires further investigations of the pharmacological activity, based on the metabolitetropic mechanisms. In addition, transformation of 3.1–3.20 in corresponding *s*-triazolo[*c*]-quinazolines with subsequent removal of protective groups

may be considered as promising pathway of chemical optimization. Modified 2-([1,2,4]triazolo[*c*]quinazoline-2-yl-)alkyl-(alkaryl-,aryl-)amines are the promising and insufficient known class of compounds, that is a valid reason for their pharmacological activity research.

Conclusions

1. The synthetic approach for the synthesis of 3*H*-quinazoline-4-ylidene)hydrazides *N*-protected amino-acids, based on the interaction of 4-hydrazinoquinazoline and corresponding imidazolides obtained *in situ* was elaborated. It was found, that benzoyl- and Boc-amino-acids were the most reliable substrates for the synthesis of the corresponding hydrazides.

2. A detailed analysis of the ^{1}H NMR spectra allowed to establish unambiguously, that of (3*H*-quinazoline-4-ylidene) hydrazides *N*-protected aminoacids in DMSO solutions are characterized by amid-imide tautomerism due to the presence of hydrazide and amide groups.

3. Synthesized compounds exhibited high antiradical activity, which showed perspectives of further screening for other types of biological activity of abovementioned objects.

4. The antibacterial activity of the synthesized compounds was evaluated by serial dilution method and it was found, that they exhibited high antimicrobial activity against *P. aeruginosa* (MIC 50–100 μg/ml and MBC 100 μg/ml) and antifungal activity against *C. albicans* (MIC 50 μg/ml, MBC 50–100 μg/ml).

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Information about authors:
Martynenko Yu. V., Postgraduate Student of the Department of Organic and Bioorganic Chemistry, Zaporizhzhia State Medical University, Ukraine.
Kazunin M. S., PhD, Senior Lecturer of the Department of Organic and Bioorganic Chemistry, Zaporizhzhia State Medical University, Ukraine.
Nosulenko I. S., PhD, Assistant of the Department of Pharmacognosy, Pharmacology and Botany, Zaporizhzhia State Medical University, Ukraine.
Berest G. G., PhD, Associate Professor of the Department of Pharmacognosy, Pharmaceutical Chemistry and Medical Preparations Technology of FPE, Zaporizhzhia State Medical University, Ukraine.
Kovalenko S. I., Dr.hab, Professor, Head of the Department of Organic and Bioorganic Chemistry, Zaporizhzhia State Medical University, Ukraine.
Kamyshnyi O. M., MD, PhD, DSci, Professor, Head of the Department of Microbiology, Virology and Immunology, Zaporizhzhia State Medical University, Ukraine.
Polishchuk N. M., MD, PhD, Senior Lecturer, Department of Microbiology, Virology and Immunology, Zaporizhzhia State Medical University, Ukraine.

Відомості про авторів:
Мартиненко Ю. В., аспірант каф. органічної і біоорганічної хімії, Запорізький державний медичний університет, Україна.
Казунін М. С., канд. фарм. наук, старший викладач каф. органічної і біоорганічної хімії, Запорізький державний медичний університет, Україна.
Носуленко І. С., канд. фарм. наук, асистент каф. фармакогнозії, фармакології та медичної ботаніки, Запорізький державний медичний університет, Україна.
Берест Г. Г., канд. фарм. наук, доцент каф. фармакогнозії, фармацевтичної хімії і технології ліків ФПО, Запорізький державний медичний університет, Україна.
Коваленко С. І., д-р фарм. наук, професор, зав. каф. органічної і біоорганічної хімії, Запорізький державний медичний університет, Україна.
Камишний О. М., д-р мед. наук, професор, зав. каф. мікробіології, вірусології та імунології, Запорізький державний медичний університет, Україна.
Поліщук Н. М., канд. мед. наук, старший викладач каф. мікробіології, вірусології та імунології, Запорізький державний медичний університет, Україна.

Сведения об авторах:
Мартыненко Ю. В., аспирант каф. органической и биоорганической химии, Запорожский государственный медицинский университет, Украина.
Казунин М. С., канд. фарм. наук, старший преподаватель каф. органической и биоорганической химии, Запорожский государственный медицинский университет, Украина.
Носуленко И. С., канд. фарм. наук, ассистент каф. фармакогнозии, фармакологии и медицинской ботаники, Запорожский государственный медицинский университет, Украина.
Берест Г. Г., канд. фарм. наук, доцент каф. фармакогнозии, фармацевтической химии и технологии лекарств ФПО, Запорожский государственный медицинский университет, Украина.
Коваленко С. И., д-р фарм. наук, профессор, зав. каф. органической и биоорганической химии, Запорожский государственный медицинский университет, Украина.
Камышный А. М., д-р мед. наук, профессор, зав. каф. микробиологии, вирусологии и иммунологии, Запорожский государственный медицинский университет, Украина.
Полищук Н. М., канд. мед. наук, старший преподаватель каф. микробиологии, вирусологии и иммунологии, Запорожский государственный медицинский университет, Украина.

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