

# Triazolo[1,5-c]quinazolines. Synthesis, antimicrobial and antifungal activity [quinazolin-4(3H)-ylidene]hydrazides of carboxylic acids (Message 1)

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The modern standards and algorithms of antimicrobial therapy, that ensure a high level of the treatment's quality and prevention of the most infectious-inflammatory diseases, provide wide using of chemotherapeutic agents. However, the modern medicines do not always have satisfactory chemotherapeutic and pharmacological properties; this fact is most often associated with the resistance of microorganisms to them. That is why the creation of the new chemotherapeutic drugs by natural antibiotics' chemical and microbiological modification, the chemical synthesis of the new substances among the various classes of organic compounds is a topical problem.

**The aim of the study** is the developing of simple and accessible methods for the synthesis of new [quinazolin-4(3H)-ylidene]hydrazides of cycloalkyl-(hetaryl) carboxylic acids, analysis of their physical-chemical properties, antimicrobial and antifungal activity.

**Materials and methods.** The study of the antimicrobial activity of synthesized compounds was carried out by the method of two-fold serial dilutions in the Mueller Hinton broth (for strains *Staphylococcus aureus* ATCC 25923, *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853) and in the Saburo broth (for *Candida albicans* ATCC 885-653). Minimal inhibitory concentration, minimal bactericidal and fungicidal concentration were defined.

**Results.** It was found that synthesized compounds show antimicrobial and antifungal activity to researched strains.

**Conclusions.** There have been considered a number of preparative methods for the synthesis of [quinazolin-4(3H)-ylidene]hydrazides of cycloalkyl-(hetaryl)carboxylic acids, which are significant as chemical reagents for the preparation of condensed heterocyclic and biologically active compounds. The structure and individuality have been proved by elementary analysis and physical-chemical methods (<sup>1</sup>H NMR-spectroscopy, HPLC/MS). The antimicrobial analysis shows that N'-[quinazolin-4(3H)-ylidene]-2(3)-heteril hydrazides containing a pyridinecarboxylic acid residue in the molecule have the highest activity, which exceeds the activity of the reference standard "Trimethoprim". N'-(6-bromohinazolin-4(3H)-ylidene)benzofuryl-2-carbohydrazide demonstrates the highest antifungal activity, which is comparable with the reference standard "Ketoconazole".

## Key words:

N'-[quinazolin-4(3H)-ylidene]carbohydrazides, synthesis, antimicrobial agents, antifungal agents.

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## Тріазоло[1,5-с]хіназоліни. Синтез, протимікробна та протигрибкова активність [хіназолін-4(3H)-іліден]гідразидів карбонових кислот (Повідомлення 1)

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Сучасні стандарти та алгоритми антимікробної терапії, що забезпечують високий рівень якості лікування та профілактики більшості захворювань інфекційно-запального характеру, передбачають широке використання хіміотерапевтичних засобів. Однак сучасні лікарські засоби не завжди мають задовільні хіміотерапевтичні та фармакологічні властивості, що найчастіше пов'язано з резистентністю мікроорганізмів до них. Саме тому створення нових хіміотерапевтичних препаратів шляхом хімічної та мікробіологічної модифікації природних антибіотиків, хімічного синтезу нових речовин серед різних класів органічних сполук є актуальною проблемою.

**Мета роботи** – розроблення простих і доступних методів синтезу нових [хіназолін-4(3H)-іліден]гідразидів циклоалкіл-(гетарил)-карбонових кислот, вивчення їхніх фізико-хімічних властивостей, дослідження протимікробної та протигрибкової активності.

**Матеріали та методи.** Протимікробну активність синтезованих хімічних сполук виконали методом дворазових серійних розведень у бульйоні Мюллера–Хінтона (для штамів *Staphylococcus aureus* ATCC 25923, *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853) і в бульйоні Сабуро (для *Candida albicans* ATCC 885–653). Визначали МІК (мінімальна інгібуєча концентрація), МБЦК і МФЦК (мінімальна бактерицидна і фунгіцидна концентрації відповідно).

**Результати.** Встановлено, що синтезовані сполуки проявляють протимікробну та протигрибкову активність до досліджуваних штамів.

**Висновки.** Розглянули препаративні методи синтезу [хіназолін-4(3H)-іліден]гідразидів циклоалкіл-(гетарил)-карбонових кислот, які є цінними хімічними реагентами для отримання конденсованих гетероциклічних і біологічно активних сполук. Будова й індивідуальність підтверджені за допомогою елементного аналізу та фізико-хімічних методів (<sup>1</sup>H ЯМР-спектроскопія, хромато-мас-спектрометрія). Аналіз результатів мікробіологічного дослідження показує, що серед синтезованих сполук найбільшу протимікробну активність мають N'-[хіназолін-4(3H)-іліден]-2(3)-гетерил-гідразиди, які містять у молекулі залишок піридинкарбонної кислоти, що перевищує активність еталону порівняння триметоприму. Найбільшу протигрибкову активність проявляє N'-(6-бромохіназолін-4(3H)-іліден)бензофуро-2-карбогідразид, який можна порівняти з еталонним порівнянням кетоконазолом.

## Ключові слова:

[хіназолін-4(3H)-іліден]гідразиди, синтез, протимікробна активність, протигрибкова активність.

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## Ключевые слова:

[хиназолин-4(3*H*)-илиден]гидразиды, синтез, противомикробная активность, противогрибковая активность.

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## Триазоло[1,5-с]хиназолины. Синтез, противомикробная и противогрибковая активность [хиназолин-4(3*H*)-илиден]гидразидов карбоновых кислот (Сообщение 1)

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Современные стандарты и алгоритмы антимикробной терапии, обеспечивающие высокий уровень качества лечения и профилактики большинства заболеваний инфекционно-воспалительного характера, предусматривают широкое использование химиотерапевтических средств. Однако современные лекарственные средства не всегда имеют удовлетворительные химиотерапевтические и фармакологические свойства, что чаще всего связано с резистентностью микроорганизмов к ним. Именно поэтому создание новых химиотерапевтических препаратов путем химической и микробиологической модификации природных антибиотиков, химического синтеза новых веществ среди различных классов органических соединений является актуальной проблемой.

**Цель работы** – разработка простых и доступных методов синтеза новых [хиназолин-4(3*H*)-илиден]гидразидов циклоалкил-(гетарил)-карбоновых кислот, изучение их физико-химических свойств, исследование противомикробной и противогрибковой активности.

**Материалы и методы.** Изучение противомикробной активности синтезированных соединений проводили методом двукратных серийных разведений в бульоне Мюллера–Хинтона (для штаммов *Staphylococcus aureus* ATCC 25923, *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853) и в бульоне Сабуро (для *Candida albicans* ATCC 885–653). Определяли МИК (минимальная ингибирующая концентрация), МБЦК и МФЦК (минимальная бактерицидная и фунгицидная концентрации соответственно).

**Результаты.** Установлено, что синтезированные соединения проявляют противомикробную и противогрибковую активность к исследуемым штаммам.

**Выводы.** Рассмотрены препаративные методы синтеза [хиназолин-4(3*H*)-илиден]гидразидов циклоалкил-(гетарил)-карбоновых кислот, которые представляют ценность как химические реагенты для получения конденсированных гетероциклических и биологически активных соединений. Строение и индивидуальность подтверждены с помощью элементного анализа и физико-химических методов (<sup>1</sup>H ЯМР-спектроскопия, хромато-масс-спектрометрия). Анализ результатов микробиологического исследования показывает, что среди синтезированных соединений наибольшую противомикробную активность проявляют *N*-[хиназолин-4(3*H*)-илиден]-2(3)-гетарил-гидразиды, содержащие в молекуле остаток пиридинкарбоновой кислоты, что превышает активность эталона сравнения триметоприма. Наибольшую противогрибковую активность проявляет *N*'-(6-бромохиназолин-4(3*H*)-илиден)бензофурил-2-карбогидразид, который сопоставим с эталоном сравнения кетоконазолом.

The modern standards and algorithms of antimicrobial therapy, that ensure a high level of the treatment's quality and prevention of the most infectious-inflammatory diseases, provide the wide using of chemotherapeutic agents.

However, the modern medicines do not always have satisfactory chemotherapeutic and pharmacological properties; this fact is most often associated with the resistance of microorganisms to them.

That is why the creation of the new chemotherapeutic drugs by natural antibiotics' chemical and microbiological modification, the chemical synthesis of the new substances among the various classes of organic compounds is a topical problem [1].

The quinazoline derivatives belong to one of the most perspective types of heterocyclic compounds that are used in modern pharmaceutical practice.

Sufficiently ample opportunity of the quinazoline cycle's chemical modification creates the significant prerequisites for the design of the new potential medical drugs [2]. The results of the previous studies [3], showed that some (3*H*-quinazolin-4-ylidene)hydrazides of carboxylic acids have the expressed antimicrobial, antifungal and other activities.

This fact substantiates the reasonability of the further researches aimed at the creation of new antimicrobial medical drugs with the greater efficiency and less toxicity in comparison with the available on the pharmaceutical market drugs.

Moreover, hydrazides of carboxylic acids are an interesting group of the organic compounds [4]. This group due to the combination of two reaction centers in the molecule is

widely used in cyclocondensation reactions for the heterocyclic systems' forming [5].

### The aim

The aim of the study is the developing of the simple and accessible methods for the synthesis of new [quinazoline-4(3*H*)-ylidene]hydrazides of cycloalkyl-(hetaryl) carboxylic acids, analysis of their physical-chemical properties, antimicrobial and antifungal activity.

### Materials and methods

**The experimental chemical part.** Melting points were determined in open capillary tubes and were uncorrected. The elemental analyses (C, H, N, S) were performed using the ELEMENTAR vario EL Cube analyzer (USA). Analyses were indicated by the symbols of the elements or functions within  $\pm 0.3\%$  of the theoretical values. The <sup>1</sup>H NMR spectra (400 MHz) and <sup>13</sup>C NMR spectra (100 MHz) were recorded on a Varian-Mercury 400 (Varian Inc., Palo Alto, CA, USA) spectrometer with TMS as the internal standard in DMSO-*d*<sub>6</sub> solution. The LC-MS were recorded using a chromat-mass spectrometric system which consisted of a high-performance liquid chromatograph "Agilent 1100 Series" (Agilent, Palo Alto, CA, USA) equipped with a diode-matrix and mass-selective detector "Agilent LC/MSD SL" (atmospheric pressure chemical ionization – APCI). The purity of all obtained compounds was checked by <sup>1</sup>H-NMR and LC-MS.

Synthesis of the derivatives of 4-hydrazinoquinazoline

(1.1–1.5) and 4-chloroquinazoline (2.1–2.5) was implemented by well-known methods, with constants that correspond to literature data [6].

*Methods of synthesis of N'-(quinazolin-4(3H)-ylidene)carbohydrazides (3.1–3.25).*

Method A. 1.95 g (11 mmol) of carbonyldiimidazole was added to the solution of 11 mmol of the corresponding carboxylic acid in 10 ml of anhydrous dioxane. The formed mixture was heated on a water bath at 60–80 °C for 1 hour, protecting from the air moisture, using tube filled by calcium chloride. Then 10 mmol of the corresponding substituted 4-hydrazinoquinazolines (1.1–1.5) were added to the reaction mixture with stirring. Then it was left for 8 hours at ambient temperature. The formed mixture was poured into water and acidified by acetic acid to pH 6–7. The formed precipitate was filtered off, dried, crystallized if necessary.

Method B. 11 mmol of the corresponding carboxylic acid hydrazide was added to the solution of 10 mmol of the corresponding substituted 4-chloroquinazoline (2.1–2.5) in 10 ml of dioxane; kept it on a water bath at 60 °C for 8 hours. After cooling, the reaction mixture was poured into water, alkalinized to pH 6–7 by 5 % sodium hydrocarbonate solute. The formed precipitate was filtered off, dried, crystallized if necessary.

*N'-(7-fluoroquinazolin-4(3H)-ylidene)cyclopropanecarbohydrazide (3.1).* Yield: 86.90 % (Method A), mp 122–124 °C; <sup>1</sup>H NMR: δ = 0.95 – 0.65 (m, 4H, cyclopropyl H-2,2', H-3,3'), 1.72–1.83 (m, 1H, cyclopropyl H-1), 6.85 (d, *J* = 7.6 Hz, 1H, H-8), 6.91 (d, *J* = 8.8 Hz, 1H, H-6), 7.97 – 7.84 (m, 1H, H-5), 8.43 (s, 1H, H-2), 10.14 (s, 1H, NH), 11.40 (s, 1H, NH); LC-MS, *m/z* = 247 [M+1]; Anal. Calcd for C<sub>12</sub>H<sub>11</sub>FN<sub>4</sub>O: C, 58.53; H, 4.50; N, 22.75; Found: C, 58.54; H, 4.49; N, 22.77.

*N'-(6-chloroquinazolin-4(3H)-ylidene)cyclopropanecarbohydrazide (3.2).* Yield: 92.12 % (Method A), mp 130–132 °C; <sup>1</sup>H NMR: δ = 0.97 – 0.63 (m, 4H, cyclopropyl H-2,2', H-3,3'), 1.67–1.84 (m, 1H, cyclopropyl H-1), 7.11 (d, *J* = 7.6 Hz, 1H, H-8), 7.33 (d, *J* = 8.2 Hz, 1H, H-5), 7.76 (d, *J* = 8.0 Hz, 1H, H-7), 8.46 (d, *J* = 7.7 Hz, 1H, H-2), 10.15 (s, 1H, NH), 11.46 (s, 1H, NH); LC-MS, *m/z* = 263 [M+1]; Anal. Calcd for C<sub>12</sub>H<sub>11</sub>ClN<sub>4</sub>O: C, 54.87; H, 4.22; N, 21.33; Found: C, 54.85; H, 4.23; N, 21.31.

*N'-(quinazolin-4(3H)-ylidene)adamantane-1-carbohydrazide (3.3).* Yield: 99.1 % (Method A), mp 221–223 °C; <sup>1</sup>H NMR: δ = 1.75 (d, *J* = 3.6 Hz, 6H, adamantyl-1 H-4,4', H-6,6', H-10,10'), 1.92 (s, 6H, adamantyl-1 H-2,2', H-8,8', H-9,9'), 2.06 (s, 3H, adamantyl-1 H-3, H-5, H-7), 7.51 – 6.88 (m, 3H, H-6, H-7, H-8), 7.72 (s, 1H, H-5), 7.93 (s, 1H, H-2), 10.01 (s, 1H, NH), 11.44 (s, 1H, NH); LC-MS, *m/z* = 323 [M+1]; Anal. Calcd for C<sub>19</sub>H<sub>22</sub>N<sub>4</sub>O: C, 70.78; H, 6.88; N, 17.38; Found: C, 70.79; H, 6.86; N, 17.38.

*N'-(8-methylquinazolin-4(3H)-ylidene)adamantane-1-carbohydrazide (3.4).* Yield: 90.95 % (Method A), mp 256–258 °C; <sup>1</sup>H NMR: δ = 1.75 (s, 9H, adamantyl-1 H-4,4', H-6,6', H-10,10', -CH<sub>3</sub>), 1.94 (s, 6H, adamantyl-1 H-2,2', H-8,8', H-9,9'), 2.17–2.02 (m, 3H, adamantyl-1 H-3, H-5, H-7), 8.63 – 6.76 (m, 4H, H-2, H-5, H-6, H-7), 9.90 (s, 1H, NH), 10.87 (s, 1H, NH); LC-MS, *m/z* = 337 [M+1]; Anal. Calcd for C<sub>20</sub>H<sub>24</sub>N<sub>4</sub>O: C, 71.40; H, 7.19; N, 16.65; Found: C, 71.39; H, 7.20; N, 16.67.

*N'-(7-fluoroquinazolin-4(3H)-ylidene)adamantane-1-carbohydrazide (3.5).* Yield: 98.9 % (Method A), mp

225–227 °C; <sup>1</sup>H NMR: δ = 2.22 – 1.55 (m, 15H, adamantyl-1 H-2,2', H-3, H-4,4', H-5, H-6,6', H-7, H-8,8', H-9,9', H-10,10'), 6.89 (d, *J* = 8.8 Hz, 1H, H-8), 7.30 (d, *J* = 7.8 Hz, 1H, H-6), 8.08 – 7.65 (m, 1H, H-5), 8.41 (s, 1H, H-2), 9.98 (s, 1H, NH), 11.48 (s, 1H, NH); LC-MS, *m/z* = 341 [M+1]; Anal. Calcd for C<sub>19</sub>H<sub>21</sub>FN<sub>4</sub>O: C, 67.04; H, 6.22; N, 16.46; Found: C, 67.03; H, 6.20; N, 16.45.

*N'-(6-chloroquinazolin-4(3H)-ylidene)adamantane-1-carbohydrazide (3.6).* Yield: 98.4 % (Method A), mp 239–241 °C; <sup>1</sup>H NMR: δ = 2.16 – 1.58 (m, 15H, adamantyl-1 H-2,2', H-3, H-4,4', H-5, H-6,6', H-7, H-8,8', H-9,9', H-10,10'), 7.13 (s, 1H, H-8), 7.95–7.58 (m, 2H, H-5, H-7), 8.44 (s, 1H, H-2), 9.98 (s, 1H, NH), 11.55 (s, 1H, NH); LC-MS, *m/z* = 357 [M+1]; Anal. Calcd for C<sub>19</sub>H<sub>21</sub>ClN<sub>4</sub>O: C, 63.95; H, 5.93; N, 15.70; Found: C, 63.96; H, 5.95; N, 15.69.

*N'-(8-methylquinazolin-4(3H)-ylidene)furan-3-carbohydrazide (3.7).* Yield: 95.42 % (Method A), mp 228–230 °C; <sup>1</sup>H NMR: δ = 2.53 (s, 3H, -CH<sub>3</sub>), 6.92 (s, 1H, furan-3-yl H-4), 7.77 – 7.10 (m, 3H, H-6,7, furan-3-yl H-5), 8.54–8.10 (m, 3H, H-2, H-5, furan-3-yl H-2), 10.24 (s, 1H, NH), 10.94 (s, 1H, NH); LC-MS, *m/z* = 269 [M+1]; Anal. Calcd for C<sub>14</sub>H<sub>12</sub>N<sub>4</sub>O<sub>2</sub>: C, 62.68; H, 4.51; N, 20.88; Found: C, 62.67; H, 4.53; N, 20.86.

*N'-(7-fluoroquinazolin-4(3H)-ylidene)furan-3-carbohydrazide (3.8).* Yield: 90.36 % (Method A), mp 236–238 °C; <sup>1</sup>H NMR: δ = 7.09 – 6.77 (m, 2H, H-6, furan-3-yl H-4), 7.29 (s, 1H, H-8), 7.57 (d, *J* = 8.0 Hz, 1H, furan-3-yl H-5), 7.87 (d, *J* = 8.1 Hz, 1H, H-5), 8.65 – 8.07 (m, 2H, H-2, furan-3-yl H-2), 10.28 (s, 1H, NH), 11.56 (s, 1H, NH); LC-MS, *m/z* = 273 [M+1]; Anal. Calcd for C<sub>13</sub>H<sub>9</sub>FN<sub>4</sub>O<sub>2</sub>: C, 57.36; H, 3.33; N, 20.58; Found: C, 57.38; H, 3.32; N, 20.57.

*N'-(6-chloroquinazolin-4(3H)-ylidene)furan-3-carbohydrazide (3.9).* Yield: 92.14 % (Method A), mp 258–260 °C; <sup>1</sup>H NMR: δ = 6.92 (s, 1H, furan-3-yl H-4), 7.16 (d, *J* = 8.8 Hz, 1H, H-8), 7.37 (d, *J* = 9.2 Hz, 1H, H-7), 7.99 – 7.51 (m, 2H, H-5, furan-3-yl H-5), 8.23 (s, 1H, H-2), 8.49 (s, 1H, furan-3-yl H-2), 10.29 (s, 1H, NH), 11.83 – 11.49 (m, 1H, NH); LC-MS, *m/z* = 289 [M+1]; Anal. Calcd for C<sub>13</sub>H<sub>9</sub>ClN<sub>4</sub>O<sub>2</sub>: C, 54.09; H, 3.14; N, 19.41; Found: C, 54.07; H, 3.15; N, 19.41.

*N'-(6-bromoquinazolin-4(3H)-ylidene)furan-3-carbohydrazide (3.10).* Yield: 76.54 % (Method A), mp 237–239 °C; <sup>1</sup>H NMR: δ = 6.91 (s, 1H, furan-3-yl H-4), 7.74 – 7.44 (m, 2H, H-7, H-8), 7.93 – 7.75 (m, 1H, furan-3-yl H-5), 7.97 (d, *J* = 3.2 Hz, 1H, H-5), 8.22 (s, 1H, H-2), 8.47 (s, 1H furan-3-yl H-2), 10.27 (d, *J* = 8.4 Hz, 1H, NH), 11.62 (s, 1H, NH); LC-MS, *m/z* = 289 [M+1]; Anal. Calcd for C<sub>13</sub>H<sub>9</sub>BrN<sub>4</sub>O<sub>2</sub>: C, 46.87; H, 2.72; N, 16.82; Found: C, 46.85; H, 2.71; N, 16.83.

*N'-(quinazolin-4(3H)-ylidene)thiophene-2-carbohydrazide (3.11).* Yield: 99.27% (Method A), 52.7 (Method B), mp 205–207 °C; <sup>1</sup>H NMR: δ = 8.46–7.07 (m, 8H, H-2, H-5, H-6, H-7, H-8, thiophene-2-yl H-3, H-4, H-5), 10.67/9.94 (b.s, 1H, NH), 11.76 (s, 1H, NH); LC-MS, *m/z* = 271 [M+1], 273 [M+3]; Anal. Calcd for C<sub>13</sub>H<sub>10</sub>N<sub>4</sub>OS: C, 57.76; H, 3.73; N, 20.73; S, 11.86; Found: C, 57.76; H, 3.71; N, 20.74; S, 11.88.

*N'-(7-fluoroquinazolin-4(3H)-ylidene)thiophene-2-carbohydrazide (3.12).* Yield: 93.65 % (Method A), mp 259–261 °C; <sup>1</sup>H NMR: δ = 6.91 (d, *J* = 8.6 Hz, 1H, H-8), 7.04 (d, *J* = 8.4 Hz, 1H, H-6), 7.33 – 7.09 (m, 1H, thiophene-2-yl H-4), 7.94 – 7.57 (m, 2H, thiophene-2-yl H-3, H-5), 8.06 (d, *J* = 8.4 Hz, 1H, H-5), 8.29 (s, 1H, H-2), 10.53/9.80 (s, 1H, NH), 11.62 (s, 1H, NH); LC-MS, *m/z* = 289 [M+1]; Anal. Calcd for C<sub>13</sub>H<sub>9</sub>FN<sub>4</sub>OS: C, 54.16; H, 3.15; F, 6.59; N, 19.43;

O, 5.55; S, 11.12; Found: C, 54.18; H, 3.14; F, 6.58; N, 19.45; O, 5.54; S, 11.11.

*N'-(8-methylquinazolin-4(3H)-ylidene)thiophene-3-carbohydrazide (3.13)*. Yield: 73.85 % (Method A), mp 228-230 °C; <sup>1</sup>H NMR: δ = 2.49 (s, 3H, CH<sub>3</sub>), 7.82 – 7.11 (m, 4H, H<sub>6</sub>, H<sub>7</sub>, thiophene-3-yl H-4, H-5), 8.56 – 7.96 (m, 3H, H-2, H-5, thiophene-3-yl H-2), 10.37 (s, 1H, NH); LC-MS, m/z = 285 [M+1]; Anal. Calcd for C<sub>14</sub>H<sub>12</sub>N<sub>4</sub>O<sub>2</sub>S: C, 59.14; H, 4.25; N, 19.70; S, 11.28; Found: C, 59.12; H, 4.26; N, 19.71; S, 11.27.

*N'-(7-fluoroquinazolin-4(3H)-ylidene)thiophene-3-carbohydrazide (3.14)*. Yield: 93.65 % (Method A), mp 228-230 °C; <sup>1</sup>H NMR: δ = 8.66 – 6.79 (m, 7H, H-2, H-5, H-6, H-8, thiophene-3-yl H-2, H-4, H-5), 10.33 (s, 1H, NH), 11.58 (s, 1H, NH); LC-MS, m/z = 285 [M+1]; Anal. Calcd for C<sub>13</sub>H<sub>9</sub>FN<sub>4</sub>O<sub>2</sub>S: C, 54.16; H, 3.15; N, 19.43; S, 11.12; Found: C, 54.15; H, 3.17; N, 19.41; S, 11.13.

*N'-(6-chloroquinazolin-4(3H)-ylidene)thiophene-3-carbohydrazide (3.15)*. Yield: 86.00 % (Method A), mp 262-264 °C; <sup>1</sup>H NMR: δ = 8.70 – 7.05 (m, 7H, H-2, H-5, H-7, H-8, thiophene-3-yl H-2, H-4, H-5), 10.41 (s, 1H, NH), 11.62 (s, 1H, NH); LC-MS, m/z = 305 [M+1]; Anal. Calcd for C<sub>13</sub>H<sub>9</sub>ClN<sub>4</sub>O<sub>2</sub>S: C, 51.24; H, 2.98; N, 18.38; S, 10.52; Found: C, 51.24; H, 2.99; N, 18.36; S, 10.53.

*N'-(6-bromoquinazolin-4(3H)-ylidene)thiophene-3-carbohydrazide (3.16)*. Yield: 65.86 % (Method A), mp 249-251 °C; <sup>1</sup>H NMR: δ = 8.75 – 7.35 (m, 7H, H-2, H-5, H-7, H-8, thiophene-3-yl H-2, H-4, H-5), 10.42 (s, 1H, NH), 11.63 (s, 1H, NH); LC-MS, m/z = 350 [M+1]; Anal. Calcd for C<sub>13</sub>H<sub>9</sub>BrN<sub>4</sub>O<sub>2</sub>S: C, 44.71; H, 2.60; N, 16.04; S, 9.18; Found: C, 44.69; H, 2.61; N, 16.03; S, 9.20.

*N'-(quinazolin-4(3H)-ylidene)benzofuran-2-carbohydrazide (3.17)*. Yield: 92.56 % (Method A), 62.5 (Method B), mp 286-288 °C; <sup>1</sup>H NMR: δ = 7.25 (d, 1H, J = 8.4 Hz, benzofuran-2-yl H-4), 7.37 (m, 2H, benzofuran-2-yl H-5, H-6), 7.50 (t, 1H, J = 7.8 Hz, H-7), 7.57 (τ, 1H, J = 7.8 Hz, H-6), 7.64 (s, 1H, benzofuran-2-yl H-3), 7.75 (d, 1H, J = 8.4 Hz, benzofuran-2-yl H-7), 7.80 (d, 1H, J = 7.8 Hz, H-8), 8.00 (d, 1H, J = 7.9 Hz, H-5), 8.12 (s, 1H, H-2), 11.03 (s, 1H, NH), 11.96 (s, 1H, NH); LC-MS, m/z = 305 [M+1]; Anal. Calcd for C<sub>17</sub>H<sub>12</sub>N<sub>4</sub>O<sub>2</sub>: C, 67.10; H, 3.97; N, 18.41; Found: C, 67.08; H, 3.98; N, 18.39.

*N'-(8-methylquinazolin-4(3H)-ylidene)benzofuran-2-carbohydrazide (3.18)*. Yield: 84.81 % (Method A), mp 284-286 °C; <sup>1</sup>H NMR: δ = 2.50 (s, 3H, CH<sub>3</sub>), 8.03 – 7.12 (m, 9H, H-2, H-5, H-6, H-7, benzofuran-2-yl H-3, H-4, H-5, H-6, H-7), 11.05 (s, 1H, NH); LC-MS, m/z = 319 [M+1]; Anal. Calcd for C<sub>18</sub>H<sub>14</sub>N<sub>4</sub>O<sub>2</sub>: C, 67.92; H, 4.43; N, 17.60; Found: C, 67.90; H, 4.43; N, 17.59.

*N'-(7-fluoroquinazolin-4(3H)-ylidene)benzofuran-2-carbohydrazide (3.19)*. Yield: 92.00 % (Method A), mp 309-311 °C; <sup>1</sup>H NMR: δ = 7.81 – 6.72 (m, 9H, H-2, H-5, H-6, H-7), 11.70 (s, 1H, NH); LC-MS, m/z = 323 [M+1]; Anal. Calcd for C<sub>17</sub>H<sub>11</sub>FN<sub>4</sub>O<sub>2</sub>: C, 63.35; H, 3.44; N, 17.38; Found: C, 63.34; H, 3.46; N, 17.37.

*N'-(6-chloroquinazolin-4(3H)-ylidene)benzofuran-2-carbohydrazide (3.20)*. Yield: 85.00 % (Method A), mp 294-296 °C; <sup>1</sup>H NMR: δ = 7.78 – 7.15 (m, 7H, H-5, H-8, benzofuran-2-yl H-3, H-4, H-5, H-6, H-7), 7.98 (d, J = 8.0 Hz, 1H, H-7), 8.43 (s, 1H, H-2), 10.90 (s, 1H, NH), 11.80 (s, 1H, NH); LC-MS, m/z = 339 [M+1]; Anal. Calcd for C<sub>17</sub>H<sub>11</sub>ClN<sub>4</sub>O<sub>2</sub>: C, 60.28; H, 3.27; N, 16.54; Found: C, 60.27; H, 3.26; N, 16.55.

*N'-(6-bromoquinazolin-4(3H)-ylidene)benzofu-*

*ran-2-carbohydrazide (3.21)*. Yield: 68.50 % (Method A), mp 267-269 °C; <sup>1</sup>H NMR: δ = 8.43 – 7.05 (m, 9H, H-2, H-5, H-7, H-8, benzofuran-2-yl H-3, H-4, H-5, H-6, H-7), 10.90 (s, 1H, NH), 11.79 (s, 1H, NH); LC-MS, m/z = 384 [M+1]; Anal. Calcd for C<sub>17</sub>H<sub>11</sub>BrN<sub>4</sub>O<sub>2</sub>: C, 53.28; H, 2.89; N, 14.62; Found: C, 53.27; H, 2.90; N, 14.64.

*N'-(quinazolin-4(3H)-ylidene)picolinohydrazide (3.22)*. Yield: 94.87 % (Method A), mp 270-272 °C; <sup>1</sup>H NMR: δ = 7.17 (d, J = 7.4 Hz, 1H, H-8), 7.36 (t, J = 7.9 Hz, 1H, H-6), 7.50 (t, J = 6.0 Hz, 1H, H-7), 7.59 (t, J = 8.2 Hz, 1H, picolinoyl H-5), 7.99 (d, J = 8.4 Hz, 1H, H-5), 8.25 (m, 1H, picolinoyl H-3,4), 8.61 (s, 1H, H-2), 8.73 (d, J = 6.6 Hz, 1H, picolinoyl H-6), 11.46 (s, 1H, NH); LC-MS, m/z = 266 [M+1]; Anal. Calcd for C<sub>14</sub>H<sub>11</sub>N<sub>5</sub>O: C, 63.39; H, 4.18; N, 26.40; Found: C, 63.41; H, 4.19; N, 26.42.

*N'-(quinazolin-4(3H)-ylidene)nicotinohydrazide (3.23)*. Yield: 98.00 % (Method A), mp 251-253 °C; <sup>1</sup>H NMR: δ = 8.44 – 7.06 (m, 7H, H-5, H-6, H-7, H-8, nicotinoyl H-3, H-4, H-5), 8.69 (s, 1H, H-2), 9.09 (s, 1H, nicotinoyl H-2), 10.72 (s, 1H, NH); LC-MS, m/z = 266 [M+1]; Anal. Calcd for C<sub>14</sub>H<sub>11</sub>N<sub>5</sub>O: C, 63.39; H, 4.18; N, 26.40; Found: C, 63.37; H, 4.19; N, 26.41.

*N'-(quinazolin-4(3H)-ylidene)isonicotinohydrazide (3.24)*. Yield: 83.30 % (Method A), mp 255-257 °C; <sup>1</sup>H NMR: δ = 8.84 – 7.05 (m, 9H, H-2, H-5, H-6, H-7, H-8, isonicotinoyl H-2, H-3, H-5, H-6), 10.76 (s, 1H, NH), 11.62 (s, 1H, NH); LC-MS, m/z = 266 [M+1]; Anal. Calcd for C<sub>14</sub>H<sub>11</sub>N<sub>5</sub>O: C, 63.39; H, 4.18; N, 26.40; Found: C, 63.36; H, 4.20; N, 26.41.

*N'-(6-bromoquinazolin-4(3H)-ylidene)isonicotinohydrazide (3.25)*. Yield: 61.01 % (Method A), mp 245-247 °C; <sup>1</sup>H NMR: δ = 8.24 – 7.49 (m, 6H, H-5, H-6, H-7, H-8, isonicotinoyl H-3, H-5), 8.49 (s, 1H, H-2), 8.71 (d, J = 8.6 Hz, 2H, isonicotinoyl H-2, H-6), 10.79 (s, 1H, NH), 11.79 (s, 1H, NH); LC-MS, m/z = 344 [M+1]; Anal. Calcd for C<sub>14</sub>H<sub>10</sub>BrN<sub>5</sub>O: C, 48.86; H, 2.93; N, 20.35; Found: C, 48.85; H, 2.92; N, 20.36.

Synthesized compounds (3.1–3.25) are white (3.1, 3.2), yellow (3.3–3.25) crystalline substances, insoluble in water, slightly soluble in alcohols, soluble in dioxane and DMF. The compounds 3.1–3.9, were purified by recrystallization from the mixture of dioxane-water (1:1), DMF-water (1:1) for the analysis.

*The experimental biological part.* The sensitivity of the microorganisms to the synthesized compounds was evaluated according the described methods [7]. The assay was conducted on Mueller–Hinton medium by two-fold serial dilution of the compound in 1 ml, after that 0.1 ml of microbial seeding (10<sup>6</sup> cells/ml) was added. The minimal inhibitory concentration of the compound was determined by the absence of visual growth in the test tube with a minimal concentration of the substance, and then the minimal bactericide/fungicide concentration was determined by the absence of growth on agar after inoculation of the microorganism from the transparent test tubes. Dimethylsulfoxide was used as a solvent, with an initial solution concentration of 1 mg/ml. Preliminary screening was performed on *Staphylococcus aureus* ATCC 25923, *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853, and *Candida albicans* ATCC 885-653 standard test cultures. Nitrofurazone, Trimetoprim and Ketoconazole were used as the reference compounds with proven antibacterial/antifungal activity. Additional quality control of the culture medium and solvents was conducted by commonly used methods [8, 9].

## Results and its discussion

Synthesis of (3H-quinazolin-4-ylidene)hydrazides cycloalkyl-(hetaryl) carboxylic acid 3.1–3.25 as the convenient precursors for the preparation of the corresponding tricyclic derivatives [10], was carried out in two alternative ways: by acylation of the corresponding substituted 4-hydrazinoquinazolines (1.1–1.5) by activated cycloalkyl-(hetaryl) carboxylic acids (Method A, *scheme 1*) and by interaction substituted 4-chloroquinazolines (2.1–2.5) with the hydrazides of the corresponding acids (Method B, *scheme 1*) [11,12]. The acylation of the compounds 1.1–1.5 was realized by imidazolides of alicyclic or heterocyclic acids (Method A). It should be noted that the regioselectivity of the reaction is determined by the place of the primary nucleophilic attack, that may be represented by the final nitrogen atom of the hydrazine moiety or by the endocyclic N (1) and N (3) atoms of quinazoline. Later, the alternative synthesis of some N-acyl derivatives (3.11, 3.17) was carried out, it was based on the interaction of substituted 4-chloroquinazolines (2.1–2.5) with hydrazides of the corresponding alicyclic acids (Method B). The using of this approach allowed the definitely establishing of the reactions' direction.

Each of the mentioned approaches has both advantages and disadvantages. Among the characteristics of the carbonyldiimidazole method, it is necessary to note the rate of performing, high yields and purity of the final products, which, in our opinion, are significant advantages, despite of the necessity of anhydrous solvents' using. One of the features of this method is the possible one-stage heterocyclization of the corresponding hydrazides into triazoloquinazoline systems, provided by the extended time and the increased temperature regime of the reaction. But the chosen reaction conditions made it possible to get the individual N'-[quinazolin-4(3H)-ylidene]-2-(3)-cycloalkyl(hetaryl)-hydrazides with the high yields.

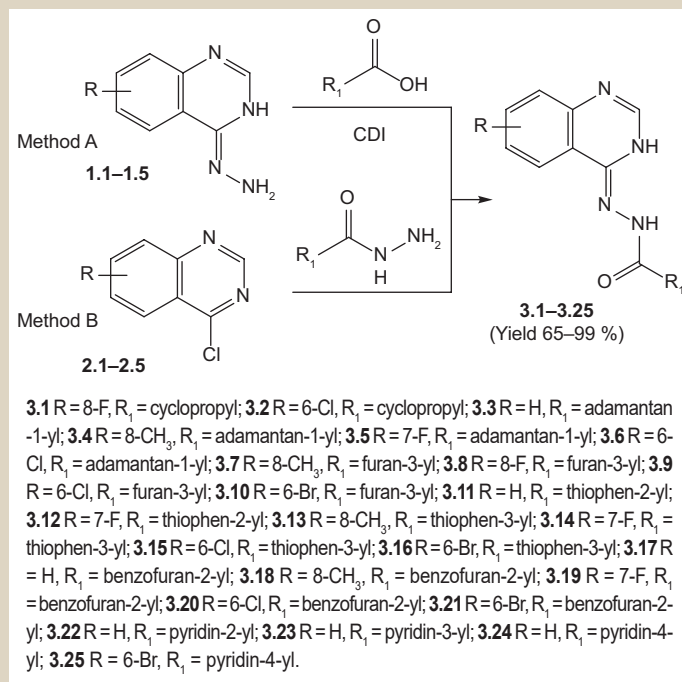
Among the disadvantage of the second method, it is necessary to note the duration of hydrazides of alicyclic or heterocyclic acids' synthesis and also the using of short-lived substituted 4-chloroquinazolines (2.1–2.5) as initial compounds.

In the LC-MS spectra (APCI) of the compounds 3.1–3.25, the signals of positive ions [M+1] were recorded which confirms the expected molecular weight of the synthesized compounds. For compounds 3.11–3.16, the signals of positive ions [M+3] were additionally recorded, which characterizes the «isotopic profile» of sulfur [13].

<sup>1</sup>H-NMR-spectra were characterized by the appearance of a low-field proton singlet of the exocyclic NH-group of the quinazoline cycle at the 11.96–10.37 ppm [11,12] and the amide NH-proton at the 11.03–9.90 ppm, which in some cases (3.13, 3.18, 3.19, 3.22, 3.23) did not appear due to rapid deuterium exchange or doubles due to hydrazide hydrazone tautomerism (3.9, 3.12). It is necessary to note that it was not possible to describe the multiplicity and characteristic chemical shifts of the aromatic protons of both quinazoline residue and the heterocyclic component of the molecule for hydrazides 3.11, 3.13–3.16, 3.18–3.21, 3.23–3.25, since they were observed as multiplets, which was a consequence of prototropic tautomerism and their significant solubility in DMSO.

In the <sup>1</sup>H NMR spectra of compounds 3.1–3.6, the signals of protons of the alicyclic residue were registered in a

Scheme 1



high field. In some cases mentioned signals were doubled, that was also caused by the tautomeric transitions. As for compounds 3.1 and 3.2 four protons of 2<sup>nd</sup> and 3<sup>rd</sup> position of the cyclopropyl moiety were registered as a multiplet at the 0.97–0.63 ppm, and the proton of 1<sup>st</sup> position as a multiplet at 1.67–1.84 ppm. The splitting of the protons of the adamantan residue of compound 3.3 was interesting: they resonated as two six-proton doublets of «bridge» protons at the 1.75 ppm (H-4.4', H-6.6', H-10.10') and the 1.92 ppm (H-2,2', H-8,8', H-9,9'), and three-proton singlet of «nodal» protons at the 2.06 ppm (H-3, H-5, H-7); for compounds 3.5 and 3.6, the protons of the adamantan residue resonated as multiplets at 2.23–1.55 ppm. In the <sup>1</sup>H NMR spectra of compounds 3.4, 3.7, 3.13, 3.18, there was a three-proton singlet of the methyl group of the position 8 at the 2.49–2.53 ppm.

It is interesting to notice that the <sup>1</sup>H-NMR spectrum of compound 3.17 made it possible to characterize both aromatic and heterocyclic protons. The aromatic protons of the quinazoline ring form the characteristic ABCD system: H-5 and H-8 were observed as doublets at the 8.00 and the 7.80 ppm respectively, and H-6 and H-7 – triplets at the 7.57 and the 7.50 ppm respectively [11,12,14]. As for proton H-2 of quinazoline cycle, it resonated as a singlet at the 8.12 ppm, that is typical for most compounds of this series [2,15]. Protons of heteryl substituents had classical chemical shifts and multiplicity [16,17].

As a result of the study of antimicrobial and antifungal activity, it was established (*Table 1*) that synthesized compounds in the concentration range of 200.0–12.5 µg/ml were active against the studied strains. The results' analysis of the effect of the test compounds on the growth of *Staphylococcus aureus* and *Escherichia coli*, showed that the greatest bacteriostatic (12.5–50.0 µg/ml) and bacteri-

**Table 1.** Antimicrobial and antifungal activity of synthesized compounds\*

Compound	Investigated strains							
	<i>Escherichia coli</i>		<i>Staphylococcus aureus</i>		<i>Pseudomonas aeruginosa</i>		<i>Candida albicans</i>	
	MIC µg/ml	MBC µg/ml	MIC µg/ml	MBC µg/ml	MIC µg/ml	MBC µg/ml	MIC µg/ml	MBC µg/ml
3.1	100	200	100	>200	50	100	50	50
3.2	100	200	100	200	50	100	200	200
3.3	200	200	50	200	100	100	50	100
3.21	100	200	50	100	100	200	25	50
3.22	50	100	12.5	50	50	100	50	100
3.23	100	100	12.5	200	100	100	50	100
Nitrofurantoin	1.5	–	6.25	–	6.25	–	25.0	–
Trimethoprim	50	50	31.2	62.5	62.5	125	62.5	125
Ketoconazole	–	–	–	–	–	–	25	–

\*: the antimicrobial and antifungal activity of other synthesized compounds is MIC-100–200 µg/ml, MBC-100–200 µg/ml, MFC-100–200 µg/ml.

dal (50–100 µg/ml) effects were exhibited by substances 3.22 and 3.23, which in hydrazide fragment contain a pyridine residue (3.22, 3.23). Towards to *Pseudomonas aeruginosa*, the investigated substances did not exhibit significant bacteriostatic and bactericidal activity (MIC-50–100 µg/ml, MBC-100–200 µg/ml).

The compound 3.21 N'-(6-bromoquinazolin-4(3H)-ylidene)benzofuryl-2-carbohydrazide (MIC 25 µg/ml, MFC 50 µg/ml) was comparable to the reference standard and exhibited the greatest antifungal activity. Interestingly, that compound 3.1 (N'-(7-fluoroquinazolin-4(3H)-ylidene)cyclopropanecarbohydrazide) did not show the activity against *Staphylococcus aureus* and *Escherichia coli* (100–200 µg/ml), but revealed bactericidal effect against *Pseudomonas aeruginosa* (MIC-50 µg/ml, MBC-100 µg/ml). The study of the fungistatic and fungicidal action of this compound against *Candida albicans* showed that it exhibited high activity (MIC and MFC 50 µg/ml). It is also necessary to mention the compounds 2.22 and 2.23, which exhibited fungicidal activity on *Candida albicans* (MIC 50 µg/ml, MFC 100 µg/ml).

So the studies of N'-[quinazolin-4(3H)-ylidene]-2(3)hydrazides antimicrobial and antifungal activity showed that the most active compounds were N'-[quinazolin-4(3H)-ylidene]-2(3)-heterylcabo-hydrazides.

## Conclusions

1. Preparative methods for the synthesis of [quinazolin-4(3H)-ylidene]hydrazides of cycloalkyl-(hetaryl) carboxylic acids are considered. The choice of presented methods depends on order of receiving of the condensed heterocyclic and biologically active compounds.

2. The individuality and structure of the synthesized compounds was confirmed by elemental analysis, <sup>1</sup>H-NMR and LC-MS spectra. It was shown, that prototropic (hydrazine-hydrazone) tautomerism is typical for synthesized compounds and, importantly, this tautomeric process leads to the changes in the integrated intensity and chemical shifts of both aromatic protons and protons of alicyclic groups.

3. The antimicrobial and antifungal activity of the new N'-[quinazolin-4(3H)-ylidene]-2(3)-cycloalkyl(hetaryl)-hydrazide derivatives was studied. It was shown, that N'-[quinazolin-4(3H)-ylidene]-2(3)-heterylcabo-hydrazides exhibited the greatest antimicrobial activity, containing a pyridine moiety in the molecule, that exceeded the activity of the trimethoprim reference standard. The greatest anti-

fungal activity was shown by N'-(6-bromoquinazolin-4(3H)-ylidene)benzofuryl-2-carbohydrazide, that is comparable to the comparison standard ketoconazole.

**Prospects for further research.** During the next stage of our studies, it is planned to establish acute toxicity indicators, as well as to study the biological activity of synthesized compounds. In addition, the obtained compounds are prospective synthons in order to receive the tricyclic derivatives.

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