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2-CYCLOALKYL-(HETARYL-)-[1,2,4]TRIAZOL[1,5-*C*]QUINAZOLINES: SYNTHESIS, PHYSICAL AND CHEMICAL PROPERTIES AND ANTIBACTERIAL ACTIVITY

Key words: synthesis, 2-cycloalkyl-(hetaryl-)-[1,2,4]triazolo[1,5-*c*]quinazolines, spectraldata, physical and chemical properties, antimicrobial and antifungal activity

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2-ЦИКЛОАЛКІЛ-(ГЕТАРИЛ-)-[1,2,4]ТРИАЗОЛО[1,5-*C*]ХІНАЗОЛІНИ: СИНТЕЗ, ФІЗИКО-ХІМІЧНІ ВЛАСТИВОСТІ ТА АНТИБАКТЕРІАЛЬНА АКТИВНІСТЬ

Ключові слова: синтез, 2-циклоалкіл-(гетарил-)-[1,2,4]триазоло[1,5-*c*]хіназоліни, спектральні дані, фізико-хімічні властивості, протимікробна та протигрибкова активність

In spite of the achievements in the chemistry of triazoloquinazolines, the synthetic possibilities of this class of compounds are not exhausted, some problems remain unresolved and require further study.2-R-[1,2,4]triazolo[1,5-*c*]quinazolines are among them due to insufficiently explored but at the same time interesting in both chemical and biological aspects. This class of compounds is actively studied for hepatoprotective, antihypoxic, antioxidant, anti-inflammatory, antitumor, antibacterial, antifungal, growth regulatory and other activities [1–4].Undoubtedly «pharmacophore» has the crucial role in the response of a biological action. It is contained in this heterocycle namely the substitute position 2.Moreover most previous studies of the authors were devoted to the insertion of alkyl, aralkyl, aryl in some cases getaryl substituents to the triazoloquinazoline cycle and to the discussion of their impact on biological activity.In fact we carried out a test of the modification of [1,2,4]triazolo[1,5-*c*]quinazolines by insertion of the methyl group or halogens (fluorine, chlorine, bromine) to the benzene moiety and by insertion of the molecule of cycloalkyl or heterocyclic substituents to the a triazole moiety.In our opinion «simple» chemical modification of the heterocycle will enhance existing types of pharmacological activity, lead to new types of biological action, improve the bioavailability of compounds by increasing the lipophilicity of molecules (in the case of cycloalkyl substituents).

Therefore the **aim** of the work is to develop simple and affordable methods for the synthesis of new ones 2-cycloalkyl-(hetaryl-)-[1,2,4]triazolo[1,5-*c*]quinazolines, study of their physical and chemical properties and primary screening for antibacterial 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 ± 0.3% of the theoretical values. The 1H NMR spectra (400 MHz) were recorded on a Varian-Mercury 400 (Varian Inc., Palo Alto, CA, USA) spectrometer with TMS as the internal standard in DMSO-*d*6 solution. The LC-MS were recorded using a chromato-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 ^{1}H-NMR and LC-MS.

(3H-Quinazolin-4-yliden)hydrazides of carboxylic acids (**1.1**–**1.36**)and4-hydrazinoquinazolines (**2.1**–**2.5**) synthesized by well-known methods [1, 3, 5].

*General methods of synthesis of 2-cycloalkyl-(hetaril-)-[1,2,4]triazolo[1,5-c] quinazolines (**3.1**–**3.36**)*

Method A. To 10 mmol (3H-quinazolin-4-yliden)hydrazides of cycloalkyl-(hetaril-)carboxylic acids (**1.1**–**1.36**) add 10 ml of glacial acetic acid and boil for 1–6 hours, the last 60 minutes distilling water from the reaction mass by the Dean-Stark nozzle. The solvent is evaporated and the residue is triturated with aqueous methanol. The residue formed is filtered off and dried.

Method B. To the 10 mmol solution of corresponding cycloalkylcarboxylic acide of 25 ml anhydrous dioxane add 1,78 g (11 mmol) *N,N′*-carbonyldiimidazole and heat in a water bath at 60–80 °C for 1 hour, protecting from the air moisture, using tube filled by calcium chloride. After that add 10 mmol the corresponding substituted 4-chloroquinazoline (**2.1**–**2.5**)to the reaction mixture with stirring and boil for 2–6 hours. The last 30–60 minutes with a Dean-Stark nozzle. The isotropic dioxane-water mixture is distilled off from the reaction mass to a volume of 10 ml. The residual solvent is distilled off under vacuum and the precipitate is triturated with water or a water-alcohol mixture. The residue of compounds 3.1–3.13 are filtered off and dried.

Compounds 3.1–3.13 obtained by methods A and B had similar physical and chemical properties and did not give a melting point depression.

2-Cyclopropyl-7-methyl-[1,2,4]triazolo[1,5-c]quinazoline (3.1). Yield: 90.9% (Method A), 81.3% (Method B), mp 103–105 °C; ^{1}H NMR: δ 1.13–1.05 (m, 4H, cyclopropyl H-2_{eq}, 3_{eq}, 2_{ex}, 3_{ex}), 2.20 (tt, 7.0, 6.2 Hz, 1H, cyclopropy lH-1), 2.73 (s, 3H, -CH_3), 7.58 (t, J = 7.6 Hz , 1H, H-9), 7.66 (d, J = 7.3 Hz, 1H, H-8), 8.20 (d, J = 7.9 Hz, 1H, H-10), 9.26 (s, 1H, H-5); LC-MS, m/z = 225 [M+1]; Anal. Calcd for $C_{13}H_{12}N_4$: C, 69.62; H, 5.39; N, 24.98; Found: C, 69.60; H, 5.40; N, 24.99.

2-Cyclopropyl-8-fluoro-[1,2,4]triazolo[1,5-c]quinazoline (3.2). Yield: 89.9% (Method A), 52.6% (Method B), mp 155–157 °C; ^{1}H NMR: δ 1.21–1.00 (m, 4H, cyclopropyl H-2_{eq}, 3_{eq}, 2_{ex}, 3_{ex}), 2.18 (tt, 7.1, 6.0 Hz, 1H, cyclopropyl H-1), 7.56 (t, J = 8.5 Hz, 1H, H-9), 7.68 (d, J = 8.7 Hz, 1H, H-7), 8.43 (dd, J = 8.7, 5.7 Hz, 1H, H-10), 9.33 (s, 1H, H-5); LC-MS, m/z = 229 [M+1]; Anal. Calcd for $C_{12}H_9FN_4$: C, 63.15; H, 3.97; N, 24.55; Found: C, 63.14; H, 5.40; N, 24.56.

9-Chloro-2-cyclopropyl-[1,2,4]triazolo[1,5-c]quinazoline (3.3). Yield: 94.5% (Method A), 87.1% (Method B), mp 149–151 °C; ^{1}H NMR: δ 1.17–1.02 (m, 4H, cyclopropyl H-2_{eq}, 3_{eq}, 2_{ex}, 3_{ex}), 2.17 (tt, 7.4, 6.1 Hz, 1H, cyclopropyl H-1), 7.79 (d, J = 8.8 Hz, 1H, H-8), 7.99 (d, J = 8.7 Hz, 1H, H-7), 8.33 (d, J = 2.5 Hz, 1H, H-10), 9.31 (s, 1H, H-5); LC-MS, m/z = 245 [M+1]; Anal. Calcd for $C_{12}H_9ClN_4$: C, 58.91; H, 3.71; N, 22.90; Found: C, 58.90; H, 3.72; N, 22.92.

2-Cyclobutyl-[1,2,4]triazolo[1,5-c]quinazoline (3.4). Yield: 79.9% (Method A), 77.3% (Method B), mp 82–84 °C; ^{1}H NMR: δ 2.18–1.99 (m, 2H, cyclobutyl H-3_{ex}, 3_{ax}), 2.63–2.32 (m, 4H, cyclobutyl H-4_{ex}, 2_{ex}, 2_{ax}, 4_{ax}), 3.86–3.72 (m, 1H, cyclobutyl H-1), 7.74 (t, J = 7.7 Hz, 1H, H-9), 7.84 (t, J = 7.9 Hz , 1H, H-8), 8.00 (d, J = 8.2 Hz, 1H, H-7), 8.44 (d, J = 7.9 Hz, 1H, H-10), 9.31 (s, 1H, H-5); LC-MS, m/z = 225 [M+1]; Anal. Calcd for $C_{13}H_{12}N_4$: C, 69.62; H, 5.39; N, 24.98; Found: C, 69.60; H, 5.40; N, 24.98.

2-Cyclobutyl-7-methyl-[1,2,4]triazolo[1,5-c] quinazoline (3.5). Yield: 99.2% (Method A), 89.4% (Method B), mp 127–128 °C; ^{1}H NMR: δ 2.23–1.94 (m, 2H, cyclobutylH-3_{ex},

3_{ax}), 2.56–2.38 (m, 4H, cyclobutyl H-4_{ex}, 2_{ex}, 2_{ax}, 4_{ax}), 2.75 (s, 3H, CH_3), 3.84–3.74 (m, 1H, cyclobutyl H-1), 7.61 (t, J = 7.7 Hz, 1H, H-9), 7.68 (d, J = 7.4 Hz, 1H, H-8), 8.27 (d, J = 7.9 Hz, 1H-10), 9.32 (s, 1H, H-5); LC-MS, m/z = 239 [M+1]; Anal. Calcd for $C_{14}H_{14}N_4$: C, 70.57; H, 5.92; N, 23.51; Found: C, 70.56; H, 5.94; N, 23.52.

2-Cyclobutyl-8-fluoro-[1,2,4]triazolo[1,5-c]quinazoline (3.6). Yield: 99.2% (Method A), 90.5% (Method B), mp 136–138 °C; ^{1}H NMR: δ 2.22–1.96 (m, 2H, cyclobutyl H-3_{ex}, 3_{ax}), 2.58–2.34 (m, 4H, cyclobutyl H-4_{ex}, 2_{ex}, 2_{ax}, 4_{ax}), 3.83–3.73 (m, 1H, cyclobutyl H-1), 7.58 (td, J = 8.7, 2.7 Hz, 1H, H-9), 7.70 (dd, J = 9.7, 2.6 Hz, 1H, H-7), 8.49 (dd, J = 8.9, 5.8 Hz, 1H, H-10), 9.38 (s, 1H, H-5); LC-MS, m/z = 243 [M+1]; Anal. Calcd for $C_{13}H_{11}FN_4$: C, 64.45; H, 4.58; N, 23.13; Found: C, 64.44; H, 4.60; N, 23.14.

2-Cyclopentyl-[1,2,4]triazolo[1,5-c]quinazoline (3.7). Yield: 98.3% (Method A), 92.8% (Method B), mp 92–94 °C; ^{1}H NMR: δ 2.22–1.62 (m, 8H, cyclopentyl H-5_{eq}, 2_{eq}, 5_{ax}, 2_{ax}, 3_{eq}, 4_{eq}, 3_{ax}, 4_{ax}), 3.39 (p, J = 8.1 Hz, 1H, cyclopentyl H-1), 7.74 (t, J = 7.6 Hz, 1H, H-9), 7.84 (t, *J* = 7.7 Hz , 1H, H-8), 8.00 (d, J = 8.2 Hz, 1H, H-7), 8.43 (d, J = 7.9 Hz, 1H, H-10), 9.30 (s, 1H, H-5); LC-MS, m/z = 239 [M+1]; Anal. Calcd for $C_{14}H_{14}N_4$: C, 70.57; H, 5.92; N, 23.51; Found: C, 70.57; H, 5.94; N, 23.50.

2-Cyclopentyl-7-methyl-[1,2,4]triazolo[1,5-c]quinazoline (3.8). Yield: 95.5% (Method A), 94.6% (Method B), mp 116–118 °C; ^{1}H NMR: δ 2.24–1.59 (m, 8H, cyclopentyl H-5_{eq}, 2_{eq}, 5_{ax}, 2_{ax}, 3_{eq}, 4_{eq}, 3_{ax}, 4_{ax}), 2.75 (s, 3H, -CH_3), 3.38 (p, J = 7.70 Hz, 1H,cyclopentyl H-1), 7.75–7.48 (m, 2H, H-8, H-9), 8.26 (t, J = 6.2 Hz, 1H, H-10), 9.31 (d, J = 4.8 Hz, 1H, H-5); LC-MS, m/z = 253 [M+1]; Anal. Calcd for $C_{15}H_{16}N_4$: C, 71.40; H, 6.39; N, 22.21; Found: C, 71.38; H, 6.40; N, 22.22.

2-Cyclopentyl-8-fluoro-[1,2,4]triazolo[1,5-c]quinazoline (3.9). Yield: 95.2% (Method A), 59.3% (Method B), mp 137–139 °C; ^{1}H NMR: δ 2.20–1.64 (m, 8H, cyclopentyl H-5_{eq}, 2_{eq}, 5_{ax}, 2_{ax}, 3_{eq}, 4_{eq}, 3_{ax}, 4_{ax}), 3.38 (p, J = 8.1 Hz, 1H, cyclopentyl H-1), 7.57 (td, J = 8.6, 2.7 Hz, 1H, H-9), 7.70 (dd, J = 9.7, 2.6 Hz, 1H, H-7),8.48 (dd, J = 8.9, 5.8 Hz, 1H, H-10), 9.37 (s, 1H, H-5); LC-MS, m/z = 257 [M+1]; Anal. Calcd for $C_{14}H_{13}FN_4$: C, 65.61; H, 5.11; N, 21.86; Found: C, 65.49; H, 5.12; N, 21.87.

9-Chloro-2-cyclopentyl-[1,2,4]triazolo[1,5-c]quinazoline (3.10). Yield: 99.2% (Method A), 83.3% (Method B), mp 105–106 °C; ^{1}H NMR: δ 2.22–1.64 (m, 8H, cyclopentyl H-5_{eq}, 2_{eq}, 5_{ax}, 2_{ax}, 3_{eq}, 4_{eq}, 3_{ax}, 4_{ax}), 3.39 (p, J = 8.0 Hz, 1H, cyclopentyl H-1), 7.82 (dd, J = 8.8, 2.5 Hz, 1H, H-8),8.01 (d, J = 8.8 Hz, 1H, H-7), 8.40 (d, J = 2.5 Hz, 1H, H-10),9.36 (s, 1H, H-5); LC-MS, m/z = 273 [M+1]; Anal. Calcd for $C_{14}H_{13}ClN_4$: C, 61.65; H, 4.80; N, 20.54; Found: C, 61.66; H, 4.82; N, 21.85.

2-*Cyclohexyl-[1,2,4]triazolo[1,5-c]quinazoline (3.11).* Yield: 99.8% (Method A), 61.4% (Method B), mp 110–112 °C; ^{1}H NMR: δ 1.42–1.39 (m, 3H, cyclohexyl H-3_{eq}, 4_{eq}, 5_{eq}), 1.81–1.60 (m, 3H, cyclohexyl H-3_{ax}, 4_{ax}, 5_{ax}), 1.97–1.81 (m, 2H, cyclohexyl H-2_{eq}, 6_{eq}), 2.09 (m, 2H, cyclohexyl H-2_{ax}, 6_{ax}), 2.94–2.89 (m, 1H, cyclohexyl H-1), 7.74 (t, J = 7.6 Hz, 1H, H-9), 7.83 (t, J = 7.8 Hz , 1H, H-8), 7.99 (d, J = 8.2 Hz, 1H, H-7), 8.42 (d, J = 7.9 Hz, 1H, H-10), 9.31 (s, 1H, H-5); LC-MS, m/z = 253 [M+1]; Anal. Calcd for $C_{15}H_{16}N_4$: C, 71.40; H, 6.39; N, 22.21; Found: C, 71.41; H, 6.40; N, 22.21.

2-Cyclohexyl-7-methyl-[1,2,4]triazolo[1,5-c]quinazoline (3.12). Yield: 99.6% (Method A), 96.3% (Method B),mp 101–103 °C; ^{1}H NMR: δ 1.81–1.28 (m, 6H, cyclohexyl H-3_{eq}, 4_{eq}, 5_{eq},3_{ax}, 4_{ax}, 5_{ax}), 1.95–1.81 (m, 2H, cyclohexyl H-2_{eq}, 6_{eq}), 2.11–2.05 (m, 2H, cyclohexyl H-2_{ax}, 6_{ax}), 2.74 (s, 3H, -CH_3), 2.99–2.87 (m, 1H, cyclohexyl H-1), 7.60 (t, J = 7.7 Hz , 1H, H-9), 7.67 (d, J = 7.3 Hz, 1H, H-8), 8.26 (d, J = 7.9 Hz, 1H, H-10), 9.32 (s, 1H, H-5); LC-MS, m/z = 267 [M+1]; Anal. Calcd for $C_{16}H_{18}N_4$: C, 72.15; H, 6.81; N, 21.04; Found: C, 72.13; H, 6.82; N, 21.05.

2-Cyclohexyl-8-fluoro-[1,2,4]triazolo[1,5-c]quinazoline (3.13). Yield: 97.9% (Method A), 93.1% (Method B), mp 169–171 °C; ^{1}H NMR: δ 1.81–1.28 (m, 6H, cyclohexyl H-3_{eq},

4_{eq}, 5_{eq},3_{ax}, 4_{ax}, 5_{ax}), 1.86–1.82 (m, 2H, cyclohexyl H-2_{eq}, 6_{eq}), 2.09–2.02 (m, 2H, cyclohexyl H-2_{ax}, 6_{ax}), 2.92–2.87 (m, 1H, cyclohexyl H-1), 7.57 (t, J = 8.8 Hz , 1H, H-9), 7.70 (d, J = 9.7 Hz, 2H, H-7), 8.47 (t, J = 7.5 Hz, 1H, H-10), 9.38 (s, 1H, H-5); LC-MS, m/z = 271 [M+1]; Anal. Calcd for $C_{15}H_{15}FN_4$: C, 66.65; H, 5.59; N, 20.73; Found: C, 66.63; H, 5.60; N, 20.74.

*2-(Adamantan-1-yl)-[1,2,4]triazolo[1,5-c]quinazoline (3.14).*Yield: 78.8% (Method A), mp 203–205 °C; ^{1}H NMR: δ 1.83 (s, 6H, adamantyl-4_{eq}, 6_{eq}, 10_{eq}, 4_{ax}, 6_{ax}, 10_{ax}), 2.03 (s, 6H, adamantyl-2_{eq}, 8_{eq}, 9_{eq}, 2_{ax}, 8_{ax}, 9_{ax}), 2.12 (s, 3H, adamantyl-3, 5, 7), 7.74 (t, J = 7.6 Hz, 1H, H-9), 7.84 (t, J = 7.7 Hz , 1H, H-8), 8.00 (d, J = 8.2 Hz, 1H, H-7), 8.45 (d, J = 7.9 Hz, 1H, H-10), 9.34 (s, 1H, H-5); LC-MS, m/z = 305 [M+1]; Anal. Calcd for $C_{19}H_{20}N_4$: C, 74.97; H, 6.62; N, 18.41; Found: C, 74.96; H, 6.64; N, 18.43.

2-(Adamantan-1-yl)-7-methyl-[1,2,4]triazolo[1,5-c]quinazoline (3.15). Yield: 98.8% (Method A), mp 245–247 °C; ^{1}H NMR: δ 1.83 (s, 6H, adamantyl-4_{eq}, 6_{eq}, 10_{eq}, 4_{ax}, 6_{ax}, 10_{ax}), 2.00 (s, 6H, adamantyl-2_{eq}, 8_{eq}, 9_{eq}, 2_{ax}, 8_{ax}, 9_{ax}), 2.12 (s, 3H, adamantyl-3, 5, 7), 2.74 (s, 3H, -CH_3), 7.60 (t, J = 7.6 Hz , 1H, H-9), 7.67 (d, J = 7.3 Hz, 1H, H-8), 8.28 (d, J = 7.9 Hz, 1H, H-10), 9.32 (s, 1H, H-5); LC-MS, m/z = 319 [M+1]; Anal. Calcd for $C_{20}H_{22}N_4$: C, 75.44; H, 6.96; N, 17.60; Found: C, 75.43; H, 6.96; N, 18.44.

2-(Adamantan-1-yl)-8-fluoro-[1,2,4]triazolo[1,5-c]quinazoline (3.16). Yield: 85.7% (Method A), mp 253–255 °C; ^{1}H NMR: δ 1.82 (s, 6H, adamantyl-4_{eq}, 6_{eq}, 10_{eq}, 4_{ax}, 6_{ax}, 10_{ax}), 2.05 (s, 6H, adamantyl-2_{eq}, 8_{eq}, 9_{eq}, 2_{ax}, 8_{ax}, 9_{ax}), 2.19 (s, 3H, adamantyl-3, 5, 7), 7.58 (t, J = 8.6 Hz , 1H, H-9), 7.70 (d, J = 9.5 Hz, 1H, H-7),8.50 (t, J = 7.6 Hz, 1H, H-10), 9.38 (s, 1H, H-5); LC-MS, m/z = 323 [M+1]; Anal. Calcd for $C_{19}H_{19}FN_4$: C, 70.79; H, 5.94; N, 17.38; Found: C, 70.77; H, 5.95; N, 17.37.

2-(Adamantan-1-yl)-9-chloro-[1,2,4]triazolo[1,5-c]quinazoline (3.17). Yield: 92.2% (Method A), mp 209–211 °C; ^{1}H NMR: δ 1.82 (s, 6H, adamantyl-4_{eq}, 6_{eq}, 10_{eq}, 4_{ax}, 6_{ax}, 10_{ax}), 2.00 (s, 6H, adamantyl-2_{eq}, 8_{eq}, 9_{eq}, 2_{ax}, 8_{ax}, 9_{ax}), 2.09 (s, 3H, adamantyl-3, 5, 7), 7.80 (d, J = 8.8 Hz, 1H, H-8), 8.00 (d, J = 8.6 Hz, 1H, H-7), 8.42 (s, 1H, H-10), 9.37 (s, 1H, H-5); LC-MS, m/z = 339 [M+1]; Anal. Calcd for $C_{19}H_{19}ClN_4$: C, 67.35; H, 5.65; N, 16.54; Found: C, 67.37; H, 5.66; N, 16.55.

2-(Adamantan-1-yl)-9-bromo-[1,2,4]triazolo[1,5-c]quinazoline (3.18). Yield: 83.0% (Method A), mp 188–190 °C; ^{1}H NMR: δ 1.81 (s, 6H, adamantyl-4_{eq}, 6_{eq}, 10_{eq}, 4_{ax}, 6_{ax}, 10_{ax}), 2.04 (s, 6H, adamantyl-2_{eq}, 8_{eq}, 9_{eq}, 2_{ax}, 8_{ax}, 9_{ax}), 2.18 (s, 9H, adamantyl-3, 5, 7), 7.94 (s, 2H, H-7,8), 8.58 (s, 1H, H-10), 9.39 (s, 1H, H-5); LC-MS, m/z = 384 [M+1]; Anal. Calcd for $C_{19}H_{19}BrN_4$: C, 59.54; H, 5.00; N, 14.62; Found: C, 59.55; H, 5.63; N, 14.64.

2-(Furan-2-yl)-[1,2,4]triazolo[1,5-c]quinazoline (3.19). Yield: 93.0% (Method A), mp 182–184 °C; ^{1}H NMR: δ 6.77 (d, J = 8.0 Hz, 1H, furan-2-yl H-3), 7.33 (t, J = 3.1 Hz, 1H, furan-2-yl H-4), 7.85 (t, J = 7.5 Hz, 1H, H-9), 8.02–7.93 (m, 2H, H-8, furan-2-yl H-5), 8.09 (d, J = 8.1 Hz, 1H, H-7), 8.50 (d, J = 7.8 Hz, 1H, H-10), 9.64 (s, 1H, H-5); LC-MS, m/z = 237 [M+1]; Anal. Calcd for $C_{13}H_8N_4O$: C, 66.10; H, 3.41; N, 23.72; Found: C, 66.08; H, 3.43; N, 23.73.

2-(Furan-3-yl)-7-methyl-[1,2,4]triazolo[1,5-c]quinazoline (3.20). Yield: 99.0% (Method A), mp 213–215 °C; ^{1}H NMR: δ 2.77 (s, 3H, -CH_3), 7.02 (d, J = 7.4 Hz, 1H, furan-3-yl H-4), 7.76–7.68 (m, 3H, H-8, H-9, furan-3-yl H-5), 8.32 (s, 2H, H-10, furan-3-yl H-2), 9.43 (s, 1H, H-5); LC-MS, m/z = 251 [M+1]; Anal. Calcd for $C_{14}H_{10}N_4O$: C, 67.19; H, 4.03; N, 22.39; Found: C, 67.18; H, 4.05; N, 22.41.

8-Fluoro-2-(furan-3-yl)-[1,2,4]triazolo[1,5-c]quinazoline (3.21). Yield: 95.9% (Method A), mp 239–241 °C; ^{1}H NMR: δ 7.02 (d, J = 7.8 Hz, 1H, furan-3-yl H-4), 7.64 (d, J = 10.2 Hz, 1H, H-9), 7.70 (s, 1H, H-7), 7.76 (d, J = 7.6 Hz, 1H, furan-3-yl H-5), 8.31 (s, 1H, furan-3-yl H-2), 8.56 (dd, J = 8.8, 5.7 Hz, 1H, H-10), 9.49 (s, 1H, H-5); LC-MS, m/z = 255 [M+1]; Anal. Calcd for $C_{13}H_7FN_4O$: C, 61.42; H, 2.78; N, 22.04; Found: C, 61.405; H, 2.80; N, 22.04.

9-Chloro-2-(furan-3-yl)-[1,2,4]triazolo[1,5-c]quinazoline (3.22). Yield: 99.6% (Method A), mp 207–209 °C; ^{1}H NMR: δ 7.01 (d, J = 7.6 Hz, 1H, furan-3-yl H-4), 7.71 (d, J = 3.6 Hz, 1H, furan-3-yl H-5), 7.85 (d, J = 8.8 Hz, 1H, H-8), 8.05 (d, J = 8.3 Hz , 1H, H-7), 8.30 (s, 1H, furan-3-yl H-2), 8.45 (d, J = 3.4 Hz, 1H, H-10), 9.47 (s, 1H, H-5); LC-MS, m/z = 271 [M+1]; Anal. Calcd for $C_{13}H_7ClN_4O$: C, 57.69; H, 2.61; N, 20.70; Found: C, 57.67; H, 2.62; N, 20.71.

9-Bromo-2-(furan-3-yl)-[1,2,4]triazolo[1,5-c]quinazoline (3.23). Yield: 92.9% (Method A), mp 210–212 °C; ^{1}H NMR: δ7.01 (d, J = 7.4 Hz 1H, furan-3-yl H-4), 7.70 (d, J = 6.8 Hz 1H, furan-3-yl H-5), 7.98 (s, 2H, H-7, H-8), 8.29 (s, 1H, furan-3-yl H-2), 8.62 (s, 1H, H-10), 9.48 (s, 1H, H-5); LC-MS, m/z = 271 [M+1]; Anal. Calcd for $C_{13}H_7BrN_4O$: C, 49.55; H, 2.24; N, 17.78; Found: C, 49.54; H, 2.25; N, 17.78.

2-(Thiophen-2-yl)-[1,2,4]triazolo[1,5-c]quinazoline (3.24). Yield: 86.4% (Method A), mp 190–192 °C; ^{1}H NMR: δ 7.30 (t, J = 4.8 Hz, 1H, thiophen-2-yl, H-4), 7.90–7.82 (m, 2H, H-9, thiophen-2-yl, H-5), 8.02–7.94 (m, 2H, H-8, thiophen-2-yl, H-3), 8.10 (d, J = 8.2 Hz, 1H, H-7), 8.52 (d, J = 8.0 Hz, 1H, H-10), 9.64 (s, 1H, H-5); LC-MS, m/z = 253 [M+1]; Anal. Calcd for $C_{13}H_8N_4S$: C, 61.89; H, 3.20; N, 22.21; S, 12.71; Found: C, 61.88; H, 3.21; N, 22.20; S, 12.70.

8-Fluoro-2-(thiophen-2-yl)-[1,2,4]triazolo[1,5-c]quinazoline (3.25). Yield: 91.3% (Method A), mp 227–228 °C; ^{1}H NMR: δ 7.20 (t, J = 4.5 Hz, 1H, thiophen-2-yl, H-4), 7.63 (q, J = 7.1, 6.6 Hz, 2H, H-9, thiophen-2-yl, H-5), 7.75 (d, J = 9.5 Hz, 1H, thiophen-2-yl, H-3), 7.90 (d, J = 3.7 Hz, 1H, H-7), 8.59 (dd, J = 9.0, 5.8 Hz, 1H, H-10), 9.50 (s, 1H, H-5); LC-MS, m/z = 271 [M+1]; Anal. Calcd for $C_{13}H_7FN_4S$: C, 57.77; H, 2.61; N, 20.73; S, 11.86; Found: C, 57.77; H, 2.60; N, 20.74; S, 11.87.

7-Methyl-2-(thiophen-3-yl)-[1,2,4]triazolo[1,5-c]quinazoline (3.26). Yield: 98.8% (Method A), mp 211–213 °C; ^{1}H NMR: δ 2.77 (s, 1H, -CH_3), 7.56 (d, J = 3.1 Hz, 1H, thiophen-3-yl, H-4), 7.65 (t, J = 7.5 Hz, 1H, H-9), 7.71 (d, J = 7.0 Hz, 1H, thiophen-3-yl, H-5), 7.78 (d, J = 5.1 Hz, 1H, H-8), 8.23 (s, 1H, thiophen-3-yl, H-2), 8.35 (d, J = 7.9 Hz, 1H, H-10), 9.43 (s, 1H, H-5), LC-MS, m/z = 267 [M+1]; Anal. Calcd for $C_{14}H_{10}N_4S$: C, 63.14; H, 3.78; N, 21.04; S, 12.04; Found: C, 63.12; H, 3.79; N, 21.02; S, 12.05.

8-Fluoro-2-(thiophen-3-yl)-[1,2,4]triazolo[1,5-c]quinazoline (3.27). Yield: 99.0% (Method A), mp 229–231 °C; ^{1}H NMR: δ 7.57 (d, J = 4.6 Hz, 1H, thiophen-3-yl, H-4), 7.70 (d, J = 4.6 Hz, 1H, thiophen-3-yl, H-5), 7.76 (t, J = 9.2 Hz, 2H, H-7, H-9), 8.24 (s, 1H, thiophen-3-yl, H-2), 8.59 (t, J = 7.4 Hz, 1H, H-10), 9.50 (s, 1H, H-5); LC-MS, m/z = 271 [M+1]; Anal. Calcd for $C_{13}H_7FN_4S$: C, 57.77; H, 2.61; N, 20.73; S, 11.86; Found: C, 57.75; H, 2.60; N, 20.75; S, 11.85.

9-Chloro-2-(thiophen-3-yl)-[1,2,4]triazolo[1,5-c]quinazoline (3.28). Yield: 71.6% (Method A), mp 198–200 °C; ^{1}H NMR: δ 7.58 (d, J = 7.7 Hz, 1H, thiophen-3-yl, H-4), 7.77 (d, J = 5.1 Hz, 1H, thiophen-3-yl, H-5), 7.85 (d, J = 8.9 Hz, 1H, H-8), 8.05 (d, J = 8.8 Hz, 1H, H-7), 8.23 (s, 1H, thiophen-3-yl, H-2), 8.48 (s, 1H, H-10), 9.48 (s, 1H, H-5); LC-MS, m/z = 287 [M+1]; Anal. Calcd for $C_{13}H_7ClN_4S$: C, 54.46; H, 2.46; N, 19.54; S, 11.18; Found: C, 54.44; H, 2.48; N, 19.53; S, 11.19.

9-Bromo-2-(thiophen-3-yl)-[1,2,4]triazolo[1,5-c]quinazoline (3.29). Yield: 99.8% (Method A), mp 189–191 °C; ^{1}H NMR: δ 7.56 (d, J = 5.1 Hz, 1H, thiophen-3-yl, H-4), 7.77 (d, J = 5.1 Hz, 1H, thiophen-3-yl, H-5), 7.98 (s, 2H, H-7, H-8), 8.23 (s, 1H thiophen-3-yl, H-2), 8.64 (s, 1H, H-10),9.49 (s, 1H, H-5); LC-MS, m/z = 332 [M+1]; Anal. Calcd for $C_{13}H_7BrN_4S$: C, 47.15; H, 2.13; N, 16.92; S, 9.68; Found: C, 47.13; H, 2.15; N, 16.93; S, 9.67.

2-(Benzofuran-2-yl)-[1,2,4]triazolo[1,5-c]quinazoline (3.30). Yield: 97.4% (Method A), mp 288–290 °C; LC-MS, m/z = 332 [M+1]; Anal. Calcd for $C_{13}H_7BrN_4S$: C, 47.15; H, 2.13; N, 16.92; S, 9.68; Found: C, 47.13; H, 2.15; N, 16.93; S, 9.67.

2-(Benzofuran-2-yl)-7-methyl-[1,2,4]triazolo[1,5-c]quinazoline(3.31). Yield: 99.2% (Method A), mp 259–261 °C; ^{1}H NMR: δ 2.78 (s, 3H, -CH_3), 7.35 (dt, *J* = 41.4, 7.5 Hz, 1H, benzofuran-2-yl H-4), 7.86 - 7.55 (m, 4H, H-8, H-9, benzofuran-2-yl H-5, H-6), 8.04 (d , J = 8.8 Hz, 2H, benzofuran-2-yl H-7), 8.22 (d, J = 3.0 Hz, 1H, benzofuran-2-yl H-3), 8.47 (d, J = 2.5 Hz, 1H, H-10),9.50 (s, 1H, H-5); LC-MS, m/z = 301 [M+1]; Anal. Calcd for $C_{18}H_{12}N_4OC$, 71.99; H, 4.03; N, 18.66; Found: C, 71.97; H, 4.05; N, 18.65.

2-Benzofuran-2-yl)-8-fluoro-[1,2,4]triazolo[1,5-c]quinazoline (3.32). Yield: 99.0% (Method A), mp 305–307 °C; ^{1}H NMR: δ 7.81–7.32 (m, 7H, H-7, H-9, benzofuran-2-yl H-3, H-4, H-5, H-6, H-7), 8.63 (s, 1H, H-10), 9.61 (s, 1H, H-5); LC-MS, m/z = 305 [M+1]; Anal. Calcd for $C_{17}H_9FN_4O$: C, 67.10; H, 2.98; N, 18.41; Found: C, 67.08; H, 2.99; N, 18.42.

2-(Benzofuran-2-yl)-9-bromo-[1,2,4]triazolo[1,5-c]quinazoline (3.33). Yield: 92.4% (Method A), mp 265–267 °C; ^{1}H NMR: δ 7.42–7.28 (s, 2H, benzofuran-2-yl H-5, H-6), 7.77–7.66 (s, 3H, benzofuran-2-yl H-3, H-4, H-7), 8.03 (s, 2H, H-7, H-8), 8.69 (s, 1H, H-10), 9.61 (s, 1H, H-5); LC-MS, m/z = 366 [M+1]; Anal. Calcd for $C_{17}H_9BrN_4O$: C, 55.91; H, 2.48; N, 15.34; Found: C, 55.90; H, 2.49; N, 15.34.

2-(1H-Indol-2-yl)-[1,2,4]triazolo[1,5-c]quinazoline (3.34). Yield: 96.2% (Method A), mp 278–280 °C; ^{1}H NMR: δ 7.08 (t, J = 7.2 Hz, 1H, 1H-indol-2-yl, H-5), 7.21 (t, J = 7.4 Hz, 1H, 1H-indol-2-yl, H-6), 7.29 (s, 1H, 1H-indol-2-yl, H-3), 7.53 (d, J = 8.0 Hz, 1H, 1H-indol-2-yl, H-4), 7.67 (d, J = 7.8 Hz, 1H, 1H-indol-2-yl, H-7), 7.87 (t, J = 7.4 Hz, 1H, H-8), 7.97 (t, J = 7.5 Hz, 1H, H-9), 8.11 (d, J = 8.0 Hz, 1H, H-7), 8.53 (d, J = 7.8 Hz, 1H, H-10), 9.65 (s, 1H, H-5), 12.09 (s, 1H, NH); LC-MS, m/z = 286 [M+1]; Anal. Calcd for $C_{17}H_{11}N_5$: C, 71.57; H, 3.89; N, 24.55; Found: C, 71.55; H, 3.91; N, 24.54.

2-(Pyridin-3-yl)-[1,2,4]triazolo[1,5-c]quinazoline (3.35). Yield: 75.7% (Method A), mp 214–216 °C; ^{1}H NMR: δ 7.53 (s, 1H, pyridin-3-yl H-5), 7.84 (t, J = 8.0 Hz, 1H, H-9), 7.92 (t, J = 7.6 Hz, 1H, H-8), 8.08 (d, J = 8.3 Hz, 1H, H-7), 8.56 (d, J = 8.5 Hz, 2H, H-10, pyridin-3-yl H-4), 8.68 (s, 1H, pyridin-3-yl H-6), 9.44 (s, 1H, pyridin-3-yl H-2), 9.52 (s, 1H, H-5); LC-MS, m/z = 248 [M+1]; Anal. Calcd for $C_{14}H_9N_5$: C, 68.01; H, 3.67; N, 28.32; Found: C, 68.00; H, 3.69; N, 28.31.

2-(Pyridin-4-yl)-[1,2,4]triazolo[1,5-c]quinazoline (3.36). Yield: 97.3% (Method A), mp 225–226 °C; ^{1}H NMR: δ 7.84 (t, J = 6.7 Hz, 1H, H-9), 7.92 (t, J = 8.7 Hz, 1H, H-8), 8.08 (d, J = 8.0 Hz, 1H, H-7), 8.17 (s, 2H, pyridin-4-yl, H-3, H-5), 8.56 (d, J = 7.8 Hz, 1H, H-10), 8.75 (s, 2H, pyridin-4-yl H-2, H-6), 9.54 (s, 1H, H-5); LC-MS, m/z = 249 [M+1]; Anal. Calcd for $C_{14}H_9N_5$: C, 68.01; H, 3.67; N, 28.32; Found: C, 68.01; H, 3.70; N, 28.30.

Synthesized compounds (**3.1**–**3.36**) are white (**3.1**–**3.17, 3.19**–**3.28, 3.34, 3.35**), yellow (**3.18, 3.29**–**3.33, 3.36**) crystalline substances, insoluble in water, sparingly soluble or soluble in alcohols, soluble dioxanes, DMF. For analysis the purified by recrystallization compounds from propanol-2 (**3.1**–**3.17**), a mixture of dioxane and water (1:1) (**3.18**–**3.29, 3.34, 3.35**), DMF-water (1:1) (**3.30**–**3.33, 3.36**) were taken.

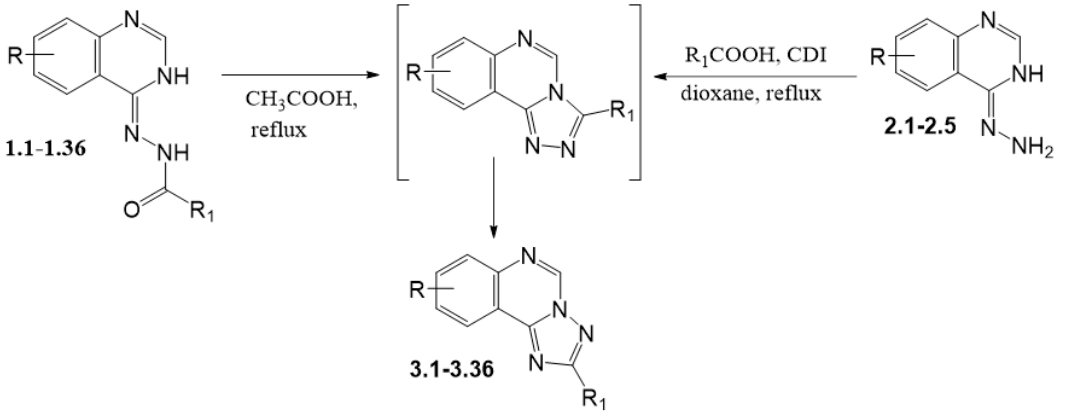
The experimental biological part

The sensitivity of the microorganisms to the synthesized compounds was evaluated according the described methods [6]. 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 (106 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. 25–100 μg/ml Nitrofural (Ltd. «Leda») and 25–100 μg/ml Ketoconazole («Hau Giang United Pharmaceutical Factory-HG Farm») 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. [7, 8].

Results and discussion

Well-known and most convenient way to obtain 2-R-[1,2,4]triazolo[1,5-*c*]quinazoline sis cyclocondensation corresponding (3*H*-quinazolin-4-yliden)hydrazides of carboxylic acids [9]. This transformation is carried out in various ways namely by thermolysis of the starting compounds, heating in glacial acetic acid, a mixture of glacial acetic acid–acetic anhydride, xylene–glacial acetic acid, phosphoryl trichloride etc [10]. We found that the optimal method for the synthesis of target compounds **3.1**–**3.36** is cyclocondensation of hydrazides **1.1**–**1.36** in acetic acid. The reaction products are chromatographically pure with yields of 78–99%. One of the features we observed upon receipt of (3*H*-quinazolin-4-yliden)hydrazides of cycloalkylcarboxylic acids (**1.1**–**1.13**) is their heterocyclization in the «carbonyldiimidazole» method of synthesis into the corresponding triazoloquinazoline systems [2]. Given the abovewe have developed «*one-pot*» synthesis of compounds **3.1**–**3.13**heterocyclization 4-hydrazinoquinazolines (**1.1**–**1.13**) with cycloalkylcarboxylic acids under these conditions. In our opinion the possibility and ease of such heterocyclization is associated with the presence of a donor substituent (cycloalkyl moiety) near the hydrazide group. Unfortunately it was not possible to obtain individual compounds **3.14**–**3.18** by this method. It is probably due to steric complications (volumetric and conformational rigid adamantane cycle).



3.1 R = 7-CH_3, R_1 = cyclopropyl; **3.2** R = 8-F, R_1 = cyclopropyl; **3.3** R = 9-Cl, R_1 = cyclopropyl; **3.4** R = H, R_1 = cyclobutyl; **3.5** R = 7-CH_3, R_1 = cyclobutyl; **3.6** R = 8-F, R_1 = cyclobutyl; **3.7** R = H, R_1 = cyclopentyl; **3.8** R = 7-CH_3, R_1 = cyclopentyl; **3.9** R = F, R_1 = cyclopentyl; **3.10** R = 9-Cl, R_1 = cyclopentyl; **3.11** R = H, R_1 = cyclohexyl; **3.12** R = 9-Cl, R_1 = cyclohexyl; **3.13** R = 8-F, R_1 = cyclohexyl; **3.14** R = H, R_1 = adamantan-1-yl; 3.**15** R = 7-CH_3, R_1 = adamantan-1-yl; **3.16** R = 8-F, R_1 = adamantan-1-yl; **3.17** R = 9-Cl, R_1 = adamantan-1-yl; **3.18** R = 9-Br, R_1 = adamantan-1-yl; **3.19** R = H, R_1 = furan-2-yl; **3.20** R = 7-CH_3, R_1 = furan-3-yl; **3.21** R = 8-F, R_1 = furan-3-yl; **3.22** R = 9-Cl, R_1 = furan-3-yl; **3.23** R = 9-Br, R_1 = furan-3-yl; **3.24** R = H, R_1 = thiophen-2-yl; **3.25** R = 8-F, R_1 = thiophen-2-yl; **3.26** R = 7-CH_3, R_1 = thiophen-3-yl; **3.27** R = 8-F, R_1 = thiophen-3-yl; **3.28** R = 9-Cl, R_1 = thiophen-3-yl; **3.29** R = 9-Br, R_1 = thiophen-3-yl; **3.30** R = H, R_1 = benzofuran-2-yl; **3.31** R = 7-CH_3, R_1 = benzofuran-2-yl; **3.32** R = 8-F, R_1 = benzofuran-2-yl; 3.**33** R = 9-Br, R_1 = benzofuran-2-yl; **3.34** R = H, R_1 = 1H-indol-2-yl; **3.35** R = H, R_1 = pyridin-3-yl; **3.36** R=H, R_1 = pyridin-4-yl

Scheme. **Synthesis of the 2-cycloalkyl-(hetaryl-)-[1,2,4]triazolo[1,5-c]quinazolines**

The heterocyclization reaction proceeds through the formation of intermediate [1,2,4] triazolo[4,3-*c*]quinazolines, which undergo recycling isomerization by the type of Dimrot

rearrangement under acid catalysis with the formation of 2-R-[1,2,4]triazolo[1,5-*c*]quinazolines (**3.1**–**3.36**) [1, 11]. In favor of the formation of this heterocycle indicate the data of ^{1}H NMR spectra of compounds **3.1**–**3.36**, namely a significant paramagnetic shift of benzene protons and the characteristic weak-field single-proton singlet of proton position 5 at 9.65–9.26 ppm.

In addition the chemical shift of the proton signal of position 5 is directly related to the donor-acceptor properties of the substituent. In the case of donor substituents (compounds **3.1**–**3.18**), this singlet resonates at 9.38–9.26 ppm, while acceptor substituents (compounds **3.19**–**3.36**) shift it to a weaker part of the spectrum [12].

Aromatic protons of the triazolo[1,5-*c*]quinazoline system (compounds **3.4, 3.7, 3.11, 3.14, 3.19, 3.24, 3.30, 3.34**–**3.36**) recorded as an ABCD system in the form of sequentially arranged doublets H-10 (8.56–8.43 ppm) and H-7 (8.11–7.99 ppm), and alsotriplets H-9 (7.85–7.74 ppm) and H-8 (7.74–7.85 ppm). Moreoverfor compounds **3.1**–**3.3, 3.5, 3.6, 3.8**–**3.10, 3.12, 3.13, 3.15**–**3.18, 3.20**–**3.23, 3.25**–**3.29, 3.31**–**3.36** that have substituents in the aromatic part of the triazolo[1,5-*c*]quinazoline system is characterized by the corresponding multiplicity and chemical shifts of the signals of aromatic and protons of the functional position substituents 2 [13].

The ^{1}H NMR spectra of compounds **3.1**–**3.18** are characterized by signals of protons of the aliphatic residue that were recorded in a strong field. The equatorial and axial protons of position 2 and 3, as well as the proton of position 1 of the cyclopropyl residue resonate as multiplets at 1.21–1.0 ppm and 2.26–2.13 ppm respectivelyin compounds **3.1**–**3.3.** A similar situation was observed in the ^{1}H NMR spectra of compounds **3.4**–**3.6**, namely the resonance of equatorial and axial protons at positions 3, 2, 4 and 1 of the cyclobutyl residue in the broad multiplets form at 2.23–1.94 ppm, 2.63–2.32 ppm and 3.86–3.72 ppm respectively. Aliphatic axial and equatorial protons, protons of cyclopentyl and cyclohexyl residues also appear in strong fields with corresponding multiplicity. The proton signals of the cyclopentane cycle (**3.7**–**3.10**) in the ^{1}H NMR spectrum were recorded as a pentet or multiplet H-1 and a wide multiplet H-5_{eq}, 2_{eq}, 5_{ax}, 2_{ax}, 3_{eq}, 4_{eq}, 3_{ax}, 4_{ax} at 3.38–3.39 ppm and at 2.24–1.59 ppm respectively. The proton H-1 of the cyclohexane substituent of compounds **3.11**–**3.13** resonates as a multiplet at 2.99–2.87 ppm, equatorial and axial protons of positions H-3, H-4 and H-5 appear by a wide multiplet at 1.81–1.28 ppm. The resonance of equatorial and axial protons H-2 and H-6 occurs by two multiplets at 1.97–1.81 ppm and 2.11–2.09 ppm respectively. The paramagnetic shift of methylene (H-1) protons in cyclobutane, cyclopentane and cyclohexane compared to cyclopropane can be explained by the non-planar structure of the cycle and as a result by the perpendicular orientation of the cycle structure relative to the direction of the magnetic field. It leads to a difference between chemical shifts of 1.2–1.0 ppm [14, 15].

An interesting cleavage is characteristic for the protons of the adamantane residue in compounds **3.14**–**3.18**. They resonate with two six-proton singlets of «bridge» protons at 1.83–1.81 ppm (H-4.4, H-6.6, H-10.10) and 2.05–2.0 ppm (H-2.2, H-8.8, H-9.9). The triproton singlet at 2.19–2.09 ppm is characteristic of for protons of «nodal» carbon atoms [16, 17]. A three-proton singlet of the methyl group of position 7 of quinazoline is observed at 2.78–2.73 ppm in the ^{1}H NMR spectra of compounds **3.1**, **3.5**, **3.8**, **3.12**, **3.15**, **3.20**, **3.26**, **3.31.**

Signals of positional getaryl substituents are observed in the strong-field part of the spectrum of compounds **3.19**–**3.36**. They have typical multiplicity and chemical shift. For example, the furan ring (compounds 3.20–3.23) in the ^{1}H NMR spectrum resonates with a single-proton singlet H-2 at 8.35–8.290 ppm and two single-proton doublets H-5 at 7.74–7.70 ppm (SCC 6.8–7.5 Hz) and H-4 at 7.02–7.01 ppm (SCC 7.4–7.8 Hz). A similar situation in the spectrum is characteristic for the protons of the thiophene cycle (compounds **3.26**–**3.29**) which resonate as single-proton doublets of H-5 at 7.77–7.70 ppm (SCC

5.1–7.0 Hz), H-4 at 7.59–7.56 ppm (SCC 3.1–4.9 Hz) and a single-proton singlet H-2 at 8.24–8.23 ppm. It should be noted that it is not possible to explain the multiplicity and typical chemical shifts of aromatic protons for both the quinazoline residue and the heterocyclic component of compounds **3.31, 3.32** due to their form of multiplets.

The ^{1}H NMR-spectrum of compound **3.34** allowed to describe both aromatic and heterocyclic protons. he indole substituent protons appear as single-proton doublets H-4 and H-7 at 7.53 ppm (SCC 8.0 Hz) and 7.67 ppm (SCC 7.8 Hz) respectively, H-5 and H-6 – triplets at 7.08 ppm (SCC 7.2 Hz) and 7.21 ppm (SCC 7.4 Hz) respectively, singlet H-3 at 7.29 ppm [13].

In the LC-MS spectra (APCI) of the compounds **3.1**–**3.36**, the signals of positive ions [M+1] were recorded which confirms the expected molecular weight of the synthesized compounds. For compounds 3.24–3.29, the signals of positive ions [M+3] were additionally recorded, which characterizes the «isotopic profile» of sulfur [18].

As we expected (Table), the results of microbiological screening demonstrated a little antimicrobial and fungicidal action in the synthesized compounds. The activity of most compounds against the main strains was observed in the concentration range of 100–200 μg/ml. However, it is necessary to distinguish compounds **3.8** and **3.14**, which inhibit the growth of *St. aureus* in MIC 25 μg/ml. A number of compounds **3.2, 3.5, 3.8, 3.10, 3.12** and **3.14** are active against *Ps.* a*eruginosa (*MIC – 50 μg/ml and MBC – 100 μg/ml).

In addition, compounds **3.2, 3.5, 3.8, 3.10, 3.12** and **3.14** show a high fungicidal effect inhibiting the growth of *C. albicans* in the concentration range of 25–100 μg/ml, approaching the strength of the effect to the reference drug «Ketonazole». Analysis of the correlationof «structure-antimicrobial activity» demonstrated that the introduction of the triazolo[1,5-*c*]quinazoline cycle, cyclopentyl (**3.8**) or adamantyl (**3.14**) substituents to position 2 is positive for the antibacterial action to *St. aureus*. The antifungal activity is determined by the cyclopentyl (**3.8**) and cyclohexyl (**3.12**) substituent of position 2 of the heterocycle, as well as the additional introduction of a methyl group in position 7.

T a b l e

Antimicrobial and antifungal activity of synthesized compounds

Compound*	Investigated strains							
	E. coli		*St. aureus*		*Ps. aeruginosa*		*C. albicans*	
	MIC μg/mL	MBC μg/mL	MIC μg/mL	MBC μg/mL	MIC μg/mL	MBC μg/mL	MIC μg/mL	MFC μg/mL
3.1	100	200	100	100	100	100	50	100
3.2	100	200	100	200	50	100	100	100
3.5	100	200	100	> 200	50	100	50	100
3.8	100	200	25	200	50	100	25	50
3.10	100	200	100	200	50	100	50	100
3.12	100	200	50	> 200	50	100	25	50
3.14	200	200	25	25	50	100	100	100
Nitrofural	1,5	–	6,25	–	6,25	–	25,0	–
Ketoconazole	–	–	–	–	–	–	25,0	–

N o t e: * 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.

Thus, microbiological studies in a number of 2-cycloalkyl-(hetaryl-)-[1,2,4] triazolo[1,5-*c*]quinazolineshave revealed a number of promising antimicrobial and antifungal agents that require further research on a wider range of strains and resistant strains of bacteria and fungi.

Prospects for further research – the next stages of the study are related to the subsequent chemical modification of the heterocycle and the study of their effect on biological parameters in other experimental pathologies (convulsions, edema, «acetic» cramps, etc.).

Conclusions

1. The optimal method of synthesis of 2-cycloalkyl-(hetaryl-)-[1,2,4]triazolo[1,5-*c*] quinazolines, which represent value as chemical reagents for further transformations and study of biological activity is substantiated and developed. The possibility of «*one-pot*» synthesis of the target compounds with 4-hydrazinoquinazolinesandcycloalkylcarboxylicac idsunder conditions of activation of the carboxyl group *N,N′*-carbonyldiimidazole is shown.

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

3. Conducted microbiological screening of 2-cycloalkyl-(hetaryl-)-[1,2,4] triazolo[1,5-c]quinazolines revealed a number of promising compounds that inhibit the growth of *St. aureus* (MIC 25–50 μg/ml) and *C. albicans* (25–50 μg/ml).

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2-CYCLOALKYL-(HETARYL-)-[1,2,4]TRIAZOLO[1,5-*c*]QUINAZOLINES: SYNTHESIS, PHYSICAL AND CHEMICAL PROPERTIES AND ANTIBACTERIAL ACTIVITY

Key words: synthesis, 2-cycloalkyl-(hetaryl-)-[1,2,4]triazolo[1,5-*c*]quinazolines, spectraldata, physical and chemical properties, antimicrobial and antifungal activity

A B S T R A C T

In spite of the achievements in the chemistry of triazoloquinazolines, the synthetic possibilities of this class of compounds are not exhausted, some problems remain unresolved and require further study. 2-R-[1,2,4] triazolo[1,5-*c*]quinazolines are among them due to insufficiently explored but at the same time interesting in both chemical and biological aspects.

Undoubtedly «pharmacophore» has the crucial role in the response of a biological action. It is contained in this heterocycle namely the substitute position 2.

In view of the above, we attempted to modify triazolo[1,5-*c*]quinazoline by introducing a methyl group or halogens (fluorine, chlorine, bromine) into a benzene moiety and a triazole moiety of a cycloalkyl or heterocyclic substituent molecule.

The aim of this work is to develop simple and affordable methods of the synthesis of new 2-cycloalkyl-(hetaryl-)-[1,2,4]triazolo[1,5-*c*]quinazolines, quinazolines, to study their physical and chemical properties and to conduct primary screening for antibacterial activity

The antimicrobial activity of the synthesized chemical compounds was performed by the method of two-fold serial dilutions in Mueller–Hinton broth (for strains of *Staphylococcus aureus* ATCC 25923, *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853) and in Saburo broth (for *Candida albicans* ATCC 885–653). MIC (minimum inhibitory concentration), MBcC and MFcC (minimum bactericidal and fungicidal concentrations respectively) was determined.

The optimal method of synthesis of 2-cycloalkyl-(hetaryl-)-[1,2,4]triazolo[1,5-*c*]quinazolines, which represent value as chemical reagents for further transformations and study of biological activity is substantiated and developed. The possibility of «*one-pot*» synthesis of the target compounds with 4-hydrazinoquinazolines and cycloalkylcarboxylic acids under conditions of activation of the carboxyl group *N,N′*-carbonyldiimidazole is shown. Conducted microbiological screening of 2-cycloalkyl-(hetaryl-)-[1,2,4]triazolo[1,5-*c*]quinazolines revealed a number of promising compounds that inhibit the growth of *St. aureus* (MIC 25–50 μg/ml) and *C. albicans* (25–50 μg/ml).

The optimal method of synthesis of 2-cycloalkyl-(hetaryl-)-[1,2,4]triazolo[1,5-*c*]quinazolin by cyclocondensation (3*H*-quinazoline-4-ylidene)hydrazides withcycloalkyl-(hetaryl)carboxylic acidsis substantiated and developed. The structure and individuality of the synthesized compounds were confirmed by elemental analysis, physicochemical methods (^{1}H NMR-spectroscopy, HPLC/MS). The peculiarity of the ^{1}H NMR spectra of this heterocycle is discussed, namely the significant paramagnetic shift of benzene protons and the characteristic weak-field single-proton singlet of the proton of position 5 of the heterocycle, which is a confirmation of recycling isomerization by Dimrot rearrangement. The structure-activity relationship is discussed and the study of the most active compounds for a wider range of strains and resistant strains of bacteria and fungi is recommended.

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2-ЦИКЛОАЛКІЛ-(ГЕТАРИЛ-)-[1,2,4]ТРИАЗОЛО[1,5-*c*]ХІНАЗОЛІНИ: СИНТЕЗ, ФІЗИКО-ХІМІЧНІ ВЛАСТИВОСТІ ТА АНТИБАКТЕРІАЛЬНА АКТИВНІСТЬ

Ключові слова: синтез, 2-циклоалкіл-(гетарил-)-[1,2,4]триазоло[1,5-*c*]хіназоліни, спектральні дані, фізико-хімічні властивості, протимікробна та протигрибкова активність

А Н О Т А Ц І Я

Незважаючи на досягнуті успіхи в хімії триазолохіназолінів, синтетичні можливості цього класу сполук не вичерпані. До маловивчених і водночас цікавих як у хімічному, так і біологічному аспекті належать 2-R-[1,2,4]триазоло[1,5-*c*]хіназоліни, які виявляють різнобічну фармакологічну активність. Безперечно, що вирішальна ключова роль у прояві тієї чи іншої біологічної дії належить «фармакофору», який міститься у даному гетероциклі, а саме замісникy у положенні 2. Враховуючи зазначене, нами здійснено спробу модифікації [1,2,4]триазоло[1,5-*c*]хіназоліну шляхом введення до бензенового фрагмента метильної групи або галогенів (флуор, хлор, бром) та до триазольного фрагмента молекули циклоалкільних або гетероциклічних замісників.

Метою роботи є розроблення простих і доступних методів синтезу нових 2-циклоалкіл-(гетарил)-[1,2,4]триазоло[1,5-*c*]хіназолінів, вивчення їхніх фізико-хімічних властивостей та виконання первинного скринінгу на антибактеріальну активність.

Протимікробну активність синтезованих хімічних сполук вивчали 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 інгібуюча концентрація), МБцК і МФцК (мінімальна бактерицидна і фунгіцидна концентрації відповідно).

Обґрунтовано та розроблено оптимальний метод синтезу 2-циклоалкіл-(гетарил-)-[1,2,4] триазоло[1,5-*c*]хіназолінів, які представляють цінність як хімічні реагенти для подальших перетворень та вивчення біологічної активності. Показана можливість «*one-pot*» синтезу цільових сполук із 4-гідразинохіназолінів та циклоалкілкарбонових кислот за умов активації карбоксильної групи *N,N′*-карбонілдіімідазолом. Виконаний мікробіологічний скринінг 2-циклоалкіл-(гетарил-)-[1,2,4] триазоло[1,5-*c*]хіназолінів дав змогу виявити ряд перспективних сполук, які інгібують ріст *St. aureus* (МІК 25–50 мкг/мл) та *C. albicans* (МІК 25–50 мкг/мл).

Обґрунтовано та розроблено оптимальний метод синтезу 2-циклоалкіл-(гетарил-)-[1,2,4] триазоло[1,5-*c*]хіназолінів циклоконденсацією (3*H*-хіназолін-4-іліден)гідразидів *із* циклоалкіл-(гетарил-)карбоновими кислотами. Структуру та індивідуальність синтезованих сполук було підтверджено елементним аналізом, фізико-хімічними методами (^{1}H ЯМР-спектроскопія, хромато-мас-спектрометрія). Обговорена особливість ^{1}H ЯМР-спектрів цього гетероциклу, а саме значний парамагнітний зсув бензенових протонів та характеристичний слабопольний однопротонний синглет протону положення 5 гетероциклу, що є підтвердженням протікання реціклізаційної ізомеризації за типом перегрупування Дімрота. Обговорено взаємозв'язок «структура–активність» та рекомендовано дослідження найактивніших сполук щодо більш широкої кількості штамів та резистентностійких штамів бактерій та грибів.

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Ключевые слова: синтез, 2-циклоалкил-(гетарил-)-[1,2,4]триазоло[1,5-*c*]хиназолины, спектральные данные, физико-химические свойства, противомикробная и протигрибковая активность

А Н Н О Т А Ц И Я

Несмотря на достигнутые успехи в химии триазолохиназолинов, синтетические возможности этого класса соединений не исчерпаны. К малоизученным и одновременно интересным как в химическом, так и биологическом аспекте принадлежат 2-R-[1,2,4]триазоло[1,5-*c*]хиназолины, которые проявляют разностороннюю фармакологическую активность. Бесспорно, что решающая ключевая роль в проявлении того или иного биологического действия принадлежит «фармакофору», который содержится в данном гетероцикле, а именно заместителю в положении 2. Учитывая указанное, нами осуществлена попытка модификации [1,2,4]триазоло[1,5-*c*]хиназолина путем введения в бензольный фрагмент метильной группы или галогенов (фтор, хлор, бром) и в триазольный фрагмент молекулы циклоалкильных или гетероциклических заместителей.

Целью работы является разработка простых и доступных методов синтеза новых 2-циклоалкил-(гетарил)-[1,2,4]триазоло[1,5-*c*]хиназолинов, изучение их физико-химических свойств и проведение первичного скрининга на антибактериальную активность.

Противомикробную активность синтезированных химических соединений изучали методом двукратных серийных разведений в бульоне Мюллера–Хинтон (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).

Обоснован и разработан оптимальный метод синтеза 2-циклоалкил-(гетарил-)-[1,2,4] триазоло[1,5-*c*]хиназолинов, которые представляют ценность как химические реагенты для дальнейших преобразований и изучения биологической активности. Показана возможность «*one-pot*» синтеза целевых соединений из 4-гидразинохиназолинов и циклоалкилкарбонових кислот в условиях активации карбоксильной группы *N,N′*-карбонилдиимидазолом. Проведенный микробиологический скрининг 2-циклоалкил-(гетарил-)[1,2,4]триазоло[1,5-*c*]хиназолинов позволил выявить ряд перспективных соединений, которые ингибируют рост *St. aureus* (МИК 25–50 мкг/мл) и *C. albicans* (МИК 25–50 мкг/мл).

Обоснован и разработан оптимальный метод синтеза 2-циклоалкил-(гетарил-)[1,2,4]триазоло[1,5-*c*] хиназолинов циклоконвденсацией (3*H*-хиназолин-4-илиден)гидразидов с циклоалкил-(гетарил-) карбоновыми кислотами. Структура и индивидуальность синтезированных соединений были подтверждены элементным анализом, физико-химическими методами (^{1}Н ЯМР-спектроскопия, хромато-масс-спектрометрия). Обсуждена особенность ^{1}Н ЯМР-спектров данного гетероцикла, а именно значительный парамагнитный сдвиг бензольных протонов и характеристический слабопольный однопротонний синглет протона положения 5 гетероцикла, что является подтверждением протекания рециклизационной изомеризации по типу перегруппировки Димрота. Обсуждены взаимосвязь «структура–активность» и рекомендовано исследование активных соединений на большем количестве штаммов и резистентноустойчивых штаммов бактерий и грибов.

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