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SYNTHESIS OF 6-CHLORO(DICHLORO-, TRICHLORO-)-METHYL-3-R-6,7-DIHYDRO-2*H*-[1,2,4]TRIAZINO[2,3-*C*]QUINAZOLIN-2-ONES AND THEIR MODIFICATION IN REACTIONS WITH NUCLEOPHILIC AND NON-NUCLEOPHILIC BASES

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The synthesis of 6-chloro-(dichloro-, trichloro)methyl-3-R-6,7-dihydro-2*H*-[1,2,4]triazino[2,3-*c*]quinazolin-2-ones and their modification under the action of nucleophilic and/or basic reagents are described in this article. It was shown that 6-chloro-(dichloro-, trichloro)methyl-3-R-6,7-dihydro-2*H*-[1,2,4]triazino[2,3-*c*]quinazolin-2-ones can be prepared by cyclocondensation of 3-(aminophenyl)-6-R-1,2;4-triazine-5(2*H*)-ones with chloro-(dichloro-)acetaldehyde or chloral hydrate. The reactivity of the synthesized compounds toward nucleophilic base morpholine and non-nucleophilic base diisopropylethylamine (DIPEA) under different conditions was studied. It was shown that the prepared compounds under the action of morpholine and/or DIPEA can be converted into the products of substitution, elimination or elimination followed by isomerization and substitution. Refluxing of 6-(chloromethyl)-3-R-6,7-dihydro-2*H*-[1,2,4]triazino[2,3-*c*]quinazoline-2-ones with equimolar quantity of morpholine and 10% excess of DIPEA in ethylene glycol monoethyl ether (EGEE) yielded the products on N-alkylation. 6-(Morpholinomethyl)-3-R-2*H*-[1,2,4]triazino[2,3-*c*]quinazoline-2-ones were obtained by heating of 6-dichloromethyl-3-R-6,7-dihydro-2*H*-[1,2,4]triazino[2,3-*c*]quinazoline-2-ones with five-fold excess of morpholine in EGEE. Reaction of 3-R-6-(trichloromethyl)-6,7-dihydro-2*H*-[1,2,4]triazino[2,3-*c*]quinazolin-2-ones with three-fold excess of DIPEA in EGEE yielded 3-R-2*H*-[1,2,4]triazino[2,3-*c*]quinazoline-2-ones. The physicochemical and spectral characteristics of the prepared compounds were determined and discussed.

Keywords: 6-R-3-(2-aminophenyl)-1,2,4-triazin-5(2*H*)-ones, chlorinated aldehydes and their hydrated forms, 6-chloro(dichloro-, trichloro-)-methyl-3-R-6,7-dihydro-2*H*-[1,2,4]triazino[2,3-*c*]quinazolin-2-ones, nucleophilic and non-nucleophilic bases, synthesis.

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Introduction

Heterocyclic compounds with halogen-substituted alkyl fragments are important class of reagents that easily interact with nucleophiles and widely used in medicinal chemistry as initial compounds for further modification [1]. The synthesis of aforementioned compounds can be conducted by halogenation of alkyl-substituted derivatives or transformation of other functional groups. Listed above processes have the disadvantages including the usage of toxic reagents and low regioselectivity. Cyclocondensation of NCCCN-nucleophiles with halogen-containing reagents (halogen-substituted aldehydes, halogen-substituted acids and their derivatives) can be considered as a promising alternative approach for the synthesis of heterocyclic compounds with halogen-substituted alkyl fragments [2,3]. These methods have undeniable advantages when possibility of variation of halogen atoms quantity and saturation state of the cycle are required. The obtained halogen-containing compounds are flexible objects for modification aimed to the synthesis of biologically active compounds. It should be noted that the choice of reaction conditions used for transformation of heterocyclic compounds with halogen-substituted alkyl fragments significantly depends on the quantity of the halogens and saturation state of the cycle. Thus, monohalogenalkyl

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derivatives react with nucleophiles by the nucleophilic substitution mechanism. For instance, 6-(chloromethyl)-3-R_1-2*H*-[1,2,4]triazino[2,3-*c*]quinazoline-2-ones in reactions with saturated azaheterocycles yielded corresponding 6-heterylmethyl-substituted derivatives [4]. The features of trichloromethyl substituted heterocycles reactivity were studied as well [5–8]. Specifics of interaction between abovementioned compounds and nucleophiles were revealed and it was shown that the reactions proceed via S_{NAr}- and *tele*-S_N-mechanism and yield corresponding heterocyclic systems [5–8]. Kholodnyak et al. [2] studied the reactivity of 2-phenyl-5-trichloromethyl-5,6-dihydro[1,2,4]triazolo[1,5-*c*]quinazoline towards *N*-nucleophiles and showed that initial compound underwent b-elimination under E_{1cb}-mechanism what resulted in the formation of 2-phenyl-5-(dichloromethyl)-[1,2,4]triazolo[1,5-*c*]quinazoline. Nevertheless, the systematic studies of the reactivity of compounds that contain mono-, di-, trihalogenalkyl substituent at the partially hydrogenated heterocyclic system were not conducted.

Therefore, this work was aimed at synthesizing 6-chloro-(dichloro-, trichloro)methyl-3-R-6,7-dihydro-2*H*-[1,2,4]triazino[2,3-*c*]quinazolin-2-ones and studying their reactivity towards morpholine, non-nucleophilic base diisopropylethylamine (DIPEA) and their mixtures under different conditions.

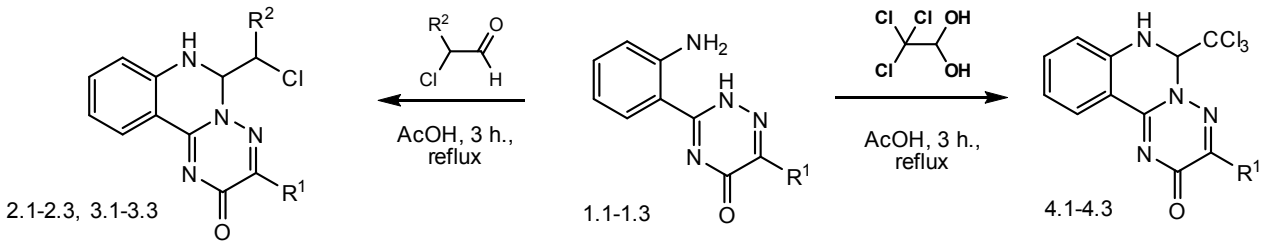
Results and discussion

It was found that refluxing of 3-(aminophenyl)-6-R-1,2,4-triazine-5(2*H*)-ones [9] (1.1–1.3) with chloroacetaldehyde (as 50% aqueous solution) and dichloroacetaldehyde in acetic acid during 3 hrs resulted in the formation of individual 6-chloro-(2.1–2.3) and 6-dichloro-(3.1–3.3)-methyl-3-R-6,7-dihydro-2*H*-[1,2,4]triazino[2,3-*c*]quinazoline-2-ones (Fig. 1) [10]. In addition, anilines 1 react with chloral hydrate to yield the compounds 4.1–4.3. It should be mentioned that the synthesis of compounds 2 and 3 by the interaction of initial compound 1.1–1.3 with 2-chloro-1,1-dimethoxyethan or 1,1-dichloro-2,2-dimethoxyethan was not successful.

Subsequently, the interactions of obtained 6-chloro-(dichloro-, trichloro-)methyl-3-R-6,7-dihydro-2*H*-[1,2,4]triazino[2,3-*c*]quinazolin-2-ones (2.1–2.3, 3.1–3.3, and 4.1–4.3) with morpholine, non-nucleophilic base diisopropylethylamine (DIPEA) and their combination were studied under various conditions. It was found that long-term heating (more than 10 hours) of compounds 2 with equimolar quantities of morpholine or DIPEA did not lead to any modification products. At the same time, refluxing of compounds 2 with equimolar quantity of morpholine and 10% excess of DIPEA in ethylene glycol monoethyl ether (EGEE) yielded the products on *N*-alkylation (5.1–5.3, Fig. 2). In addition, it was established that the presence of DIPEA is essential for *N*-alkylation process. Thus, refluxing of compounds 1 with three-fold excess of morpholine resulted in the complex multicomponent mixtures that contained initial compounds, product of alkylation and unidentifiable compounds.

In case of 6-dichloromethyl-3-R-6,7-dihydro-2*H*-[1,2,4]triazino[2,3-*c*]quinazoline-2-ones (3.1–3.3), the products of modification, namely 6-(morpholinomethyl)-3-R-2*H*-[1,2,4]triazino-[2,3-*c*]quinazoline-2-ones (6.1–6.3), were obtained by refluxing of initial compound with five-fold excess of morpholine in EGEE (Fig. 2). The obtained compounds were formed as result of subsequent dehydrohalogenation, isomerization and nucleophilic substitution. The usage of equimolar quantity of morpholine, 10% excess of DIPEA or their mixture as reagents as well as dioxane as a solvent was not reasonable. Thus, initial compounds were isolated in abovementioned conditions.

The most unexpected results were obtained in the study of 3-R-6-(trichloromethyl)-6,7-dihydro-2*H*-[1,2,4]triazino[2,3-*c*]quinazolin-2-ones (4.1–4.3)



R^1 = Ph, 4-*i*-PrC_6H_4, 4-FC_6H_4; R^2 = H, Cl

Fig. 1. Reaction of 6-R-3-(2-aminophenyl)-2*H*-[1,2,4]triazone-5-oneas with halogen-containing aldehydes and their hydrated forms

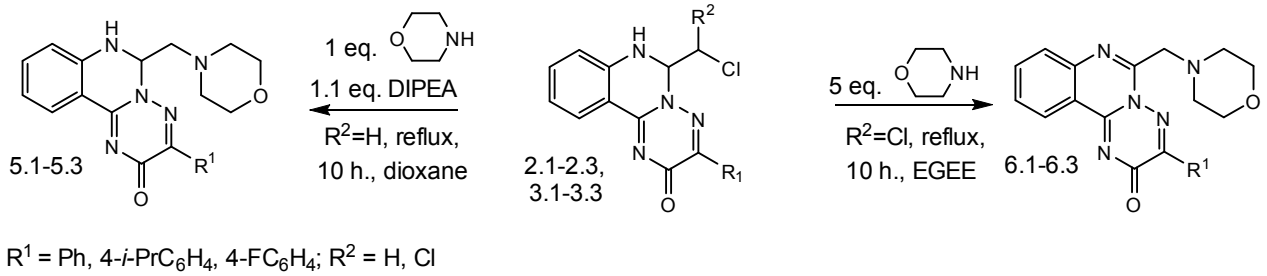


Fig. 2. The reactivity of 6-chloromethyl- and 6-dichloromethyl-3-R-6,7-dihydro-2*H*-[1,2,4]triazino[2,3-*c*]quinazoline-2-ones towards DIPEA and/or morpholine

reactivity towards morpholine or DIPEA. It was established that refluxing of compounds 4.1–4.3 with three-fold excess of DIPEA resulted in the elimination of trichlormethane and formation of 3-R-2*H*-[1,2,4]triazino[2,3-*c*]quinazoline-2-ones (7.1–7.3, Fig. 3). Compounds 7.1–7.3 were also identified as minor components of the mixtures formed as result of long-term heating of equimolar quantities of compounds 4.1–4.3, morpholine and DIPEA in dioxane. The main products of aforementioned reaction were compounds 8.1–8.3 that were formed as result of dehydrohalogenation followed by isomerization. Besides, it was shown that refluxing of compounds 4.1–4.3 with excess of morpholine in dioxane resulted in the formation of complex mixtures of unidentifiable products.

The main features of the reactions between 6-chloro-(dichloro-, trichloro-)methyl-3-R-6,7-dihydro-2*H*-[1,2,4]triazino[2,3-*c*]quinazoline-2-ones and morpholine, DIPEA or their combination are summarized in Table.

The purity of the synthesized compounds and

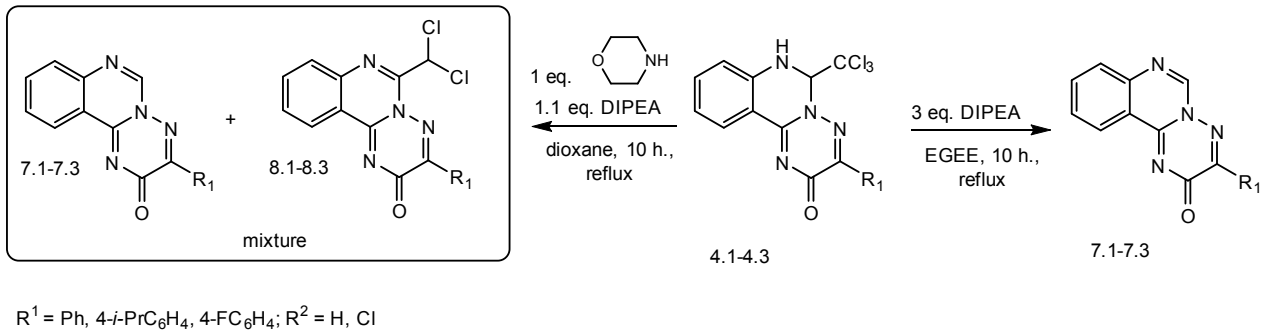


Fig. 3. The features of 3-R-6-(trichloromethyl)-6,7-dihydro-2*H*-[1,2,4]triazino[2,3-*c*]quinazolin-2-ones transformations under the action of morpholine or/and DIPEA

The features of the reactions between 6-chloro-(dichloro-, trichloro-)methyl-3-R-6,7-dihydro-2*H*-[1,2,4]triazino-[2,3-*c*]quinazoline-2-ones and morpholine, DIPEA or their combination

Initial compounds	Reagents	Solvent	Resulting products
2.1–2.3	morpholine (1 eq.)	dioxane	initial compounds
	DIPEA (1.1 eq.)	dioxane or EGEE	initial compounds
	morpholine (3 eq.)	EGEE	unidentifiable products mixture
	morpholine (1 eq.) and DIPEA (1.1 eq.)	dioxane	5.1–5.3
3.1–3.3	morpholine (1 eq.)	dioxane	initial compounds
	DIPEA (1.1 eq.)	dioxane or EGEE	initial compounds
	morpholine (5 eq.)	EGEE	6.1–6.3
	morpholine (1 eq.) and DIPEA (1.1 eq.)	dioxane	initial compounds
4.1–4.3	DIPEA (3 eq.)	EGEE	7.1–7.3
	morpholine (7 eq.)	dioxane	unidentifiable products mixture
	morpholine (1 eq.) and DIPEA (1.1 eq.)	dioxane	compounds 7 and 8 mixture

the composition of the obtained mixtures were proven by LC-MS and ^{1}H NMR and IR-spectrometry. The signals with *m/z* values that correspond to the proposed structures were observed in LC-MS spectra of the synthesized compounds.

The ^{1}H NMR spectra of compounds 2, 3 and 4 were characterized by the signals of NH-proton in 7th position that were observed as doublets or multiplets at 7.75–7.80 ppm, 8.05–8.22 ppm and 8.68–8.97 ppm for compounds 2.1–2.3, 3.1–3.3 and 4.1–4.3, respectively. The signals of proton in 6th position were registered at 5.82–5.86 ppm (compounds 2.1–2.3), 6.01–6.04 ppm (compounds 3.1–3.3) and 6.36–6.55 ppm (compounds 4.1–4.3). Compounds 2.1–2.3 and 3.1–3.3 were additionally characterized by signals of substituent in 6th position, namely two-proton doublet of doublets at 3.88–3.90 ppm (compounds 2.1–2.3) or one proton doublet at 6.38–6.43 (compounds 3.1–3.3). The series of multiplets that correspond to the morpholine moiety were characteristic for ^{1}H NMR spectra of compounds 5.1–5.3 and 6.1–6.3. The signals of NH proton in 7th position and CH proton in 6th position were observed in spectra of compounds 5.1–5.3 as well. In ^{1}H NMR spectra of compounds 6.1–6.3, the signals of the positions 8, 9, 10 and 11 underwent paramagnetic shift what proved the aromatization of pyrimidine fragment. The ^{1}H spectra of compounds 7.1–7.3 were identical to the described previously [11].

Conclusions

6-Chloro(dichloro-, trichloro-)-methyl-3-R-6,7-dihydro-2*H*-[1,2,4]triazino [2,3-*c*]quinazolin-2-ones can be prepared *via* condensation of 3-(aminophenyl)-6-R-1,2,4-triazine-5(2*H*)-ones with chlorinated aldehydes or their hydrated forms. The obtained compounds under the action of morpholine and/or DIPEA undergo chemical transformation, and the structure of the products depends on the quantity of halogens, the nature or reagents and solvent, and heating regime. The prospects of 6-((chloro-(dichloro-, trichloro-)-methyl)-3-R-6,7-dihydro-2*H*-[1,2,4]triazino[2,3-*c*]-quinazoline-2-ones chemical modification have been revealed and described.

Experimental 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). ^{1}H NMR spectra (400 MHz) were recorded on a Varian-Mercury 400 (Varian Inc., Palo Alto, CA, USA) spectrometers with TMS as internal standard in DMSO-d_6 solution. LC-MS were recorded using chromatography/mass spectrometric system which consists of high performance liquid chromatography «Agilent 1100 Series» (Agilent, Palo Alto, CA, USA) equipped with diode-matrix and mass-selective detector «Agilent LC/MSD SL» (atmospheric pressure chemical ionization – APCI). Electron impact mass spectra (EI-MS) were recorded on a Varian 1200 L instrument at 70 eV (Varian, USA).

Substances 1.1–1.3 were synthesized according to the reported procedures [9]. The alternative methods of the synthesis of compounds 6.1, 6.2, and 7.1–7.3 were described elsewhere [4,11]. Other starting materials and solvents were obtained from commercially available sources and used without additional purification.

General method for synthesis of 6-((chloro-(dichloro-, trichloro-)methyl)-3-R-6,7-dihydro-2H-[1,2,4]triazino[2,3-c]quinazoline-2-ones (2.1–2.3, 3.1–3.3, 4.1–4.3)

10 mmol of chlorine containing aldehyde or chloral hydrate was added to the suspension of 10 mmol of 6-R-3-(2-aminophenyl)-1,2,4-triazine-5(2*H*)-one (1.1–1.3) in 30 ml of glacial acetic acid. The reaction mixture was refluxed for 3 hours. The solvent was evaporated under vacuum, then 30 ml of methanol was added and formed precipitate was filtered. For additional purification obtained compounds can be crystallized from dioxane.

6-(Chloromethyl)-3-phenyl-6,7-dihydro-2H-[1,2,4]triazino[2,3-c]quinazolin-2-one (2.1)

Yield: 53.8%; M.p.: 205–207^{0}C; ^{1}H NMR, δ, ppm (*J*, Hz): 3.90 (dd, 1H, *J*=11.7, *J*=5.1, –CH_2Cl), 3.99 (dd, 1H, *J*=11.7, *J*=5.1, –CH_2Cl), 5.86 (m, 1H, H-6), 6.86 (t, 1H, *J*=7.4, H-10), 6.93 (d, 1H, *J*=8.0, H-8), 7.58–7.26 (m, 4H, H-9, 3-Ar H-3,4,5), 7.80 (m, 1H, d, NH), 8.00 (d, 1H, *J*=7.5, H-11), 8.18 (d, 2H, *J*=5.6, 3-Ar H-2,6); LC-MS: *m/z*=325 [M+1], 327 [M+3]; Anal. calcd. for $C_{17}H_{13}ClN_4O$: C 62.87; H 4.03; N 17.25; Found: C 62.95; H 4.09; N 17.31.

6-(Chloromethyl)-3-(4-i-propylphenyl)-6,7-dihydro-2H-[1,2,4]triazino[2,3-c]quinazolin-2-one (2.2)

Yield: 76.8%; M.p.: 245–247^{0}C; ^{1}H NMR, δ, ppm (*J*, Hz): 1.30 (d, *J*=6.8, 6H, –CH(CH_3)$_2$), 2.98 (dt, *J*=13.6, 6.8, 1H, –CH(CH$_3$)$_2$), 3.89 (dd, *J*=11.7, 5.1, 1H, –CH_2Cl), 3.99 (dd, *J*=11.7, 5.1, 1H, –CH_2Cl), 5.84 (m, 1H, H-6), 6.85 (t, *J*=7.5, 1H, H-10), 6.92 (d, *J*=8.1, 1H, H-8), 7.30 (d, *J*=8.1, 2H, 3-Ar H-3,5), 7.39 (t, *J*=7.5, 1H, H-9), 7.77 (m, 1H, 7-NH), 8.00 (d, *J*=7.7, 1H, H-11), 8.12 (d, *J*=8.0, 2H, 3-Ar H-2,6); LC-MS: *m/z*=367 [M+1]; Anal. calcd. for $C_{20}H_{19}ClN_4O$: C 65.48; H 5.22; N 15.27; Found: C 65.57; H 5.29; N 15.34.

6-(Chloromethyl)-3-(4-fluorophenyl)-6,7-dihydro-2H-[1,2,4]triazino[2,3-c]quinazolin-2-one (2.3)

Yield: 72.0%; M.p.: 217–219°C; ^{1}H NMR, δ, ppm (*J*, Hz): 3.88 (dd, *J*=11.7, 5.1 Hz, 1H, –C*H*$_2$Cl), 3.97 (dd, *J*=11.7, 5.1 Hz, 1H, –C*H*$_2$Cl), 5.82 (m, 1H, H-6), 6.85 (t, 1H, *J*=7.1, H-10), 6.91 (d, 1H, *J*=7.9, H-8), 7.18 (t, 2H, *J*=7.9, 3-Ar 3,5), 7.38 (t, 1H, *J*=7.2, H-9), 7.75 (m, 1H, 7-NH), 8.00 (d, 1H, *J*=7.6, H-11), 8.30 (dd, 2H, 3-Ar H-2,6 Ar); LC-MS: *m/z*=343 [M+1]; Anal. calcd. for $C_{17}H_{12}ClFN_4O$: C 59.57; H 3.53; N 16.35; Found: C 59.62; H 3.64; N 16.41.

6-(Dichloromethyl)-3-phenyl-6,7-dihydro-2H-[1,2,4]triazino[2,3-c]quinazolin-2-one (3.1)

Yield: 99.3%; M.p.: 198–200°C; ^{1}H NMR, δ, ppm (*J*, Hz): 6.03 (t, *J*=4.0, 1H, H-6), 6.41 (d, *J*=4.4, 1H, –CHCl$_2$), 6.85 (t, *J*=7.4, 1H, H-10), 6.98 (d, *J*=8.1, 1H, H-8), 7.51–7.29 (m, 4H, H-9, 3-Ar H-3,4, 5), 8.00 (d, *J*=7.7, 1H, H-11), 8.05 (m, 1H, 7-NH), 8.23 (d, 2H, 3-Ar H-2,6); LC-MS: *m/z*=359 [M+1]; Anal. calcd. for $C_{17}H_{12}Cl_2N_4O$: C 56.84; H 3.37; N 15.60; Found: C 56.93; H 3.48; N 15.69.

6-(Dichloromethyl)-3-(4-isopropylphenyl)-6,7-dihydro-2H-[1,2,4]triazino[2,3-c]quinazolin-2-one (3.2)

Yield: 62.4%; M.p.: 187–189°C; ^{1}H NMR, δ, ppm (*J*, Hz): 1.28 (d, *J*=6.6, 6H, –CH(CH$_3$)$_2$), 3.01 (dt, *J*=13.4, 6.6, 1H, –CH(CH$_3$)$_2$), 6.01 (t, *J*=4.0, 1H, H-6), 6.38 (d, *J*=4.1, 1H, –C*H*Cl$_2$), 6.79 (t, *J*=7.2, 1H, H-10), 6.94 (d, *J*=8.1, 1H, H-8), 7.28 (d, *J*=8.0, 2H, 3-Ar H-3,5), 7.41 (t, *J*=7.9, 1H, H-9), 7.89 (d, *J*=7.9, 1H, H-11), 8.14 (d, *J*=8.0, 2H, 3-Ar H-2,6 Ar), 8.20 (d, *J*=3.9 Hz, 1H, 7-NH),); LC-MS: *m/z*=401 [M+1]; Anal. calcd. for $C_{20}H_{18}Cl_2N_4O$: C 59.86; H 4.52; N 13.96; Found: C 59.90; H 4.57; N 14.01.

6-(Dichloromethyl)-3-(4-fluorophenyl)-6,7-dihydro-2H-[1,2,4]triazino[2,3-c]quinazolin-2-one (3.3)

Yield: 99.5%; M.p.: 200–203°C; ^{1}H NMR, δ, ppm (*J*, Hz): 6.04 (t, *J*=4.1, 1H, H-6), 6.43 (d, *J*=4.3, 1H, –C*H*Cl$_2$), 6.85 (t, *J*=7.3, 1H, H-10), 6.98 (d, *J*=8.2, 1H, H-8), 7.20 (t, *J*=8.7, 2H, 3-Ar H-3,5), 7.40 (t, *J*=7.6, 1H, H-9), 7.99 (d, *J*=7.6, 1H, H-11), 8.22 (d, *J*=3.5, 1H, 7-NH), 8.31 (2H, dd, *J*=8.5, 5.8, 3-Ar H-2,6); LC-MS: *m/z*=377 [M+1], 379 [M+3]; Anal. calcd. for $C_{17}H_{11}Cl_2FN_4O$: C 54.13; H 2.94; N 14.85; Found: C 54.18; H 3.05; N 14.93.

6-(Trichloromethyl)-3-phenyl-6,7-dihydro-2H-[1,2,4]triazino[2,3-c]quinazolin-2-one (4.1)

Yield: 68.9%; M.p.: 235–240°C; ^{1}H NMR, δ, ppm (*J*, Hz): 6.51 (d, 1H, *J*=3.5, H-6), 6.89 (t, 1H, *J*=7.3, H-10), 7.06 (d, 1H, *J*=8.1, H-8), 7.59–7.32 (m, 4H, H-9, 3-Ar H-3,4,5), 8.02 (d, 1H, *J*=7.7, H-11), 8.17 (d, 2H, *J*=6.5, 3-Ar H-2,6 Ph), 8.68–8.97 (m, 1H, 7-NH); LC-MS: *m/z*=393 [M+1]; Anal. calcd. for $C_{17}H_{11}Cl_3N_4O$: C 51.87; H 2.82; N 14.23; Found: C 51.93; H 2.89; N 14.28.

3-(4-Isopropylphenyl)-6-(trichloromethyl)-6,7-dihydro-2H-[1,2,4]triazino[2,3-c]quinazolin-2-one (4.2)

Yield: 70.5%; M.p.: 257–259°C; ^{1}H NMR, δ, ppm (*J*, Hz): d 1.29 (d, *J*=6.7 Hz, 6H, CH(CH$_3$)$_2$), 3.10–2.83 (m, 1H, CH(CH$_3$)$_2$), 6.55–6.36 (m, 1H, H-6), 6.89 (t, *J*=7.1, 1H, H-10), 7.05 (d, *J*=8.0, 1H, H-8), 7.32 (d, *J*=7.8, 1H, 3-Ar H-3,5), 7.45 (t, *J*=7.5, 1H, H-9), 8.01 (d, *J*=7.7, 1H, H-11), 8.12 (d, *J*=7.9 , 2H, 3-Ar H-2,6), 8.80 (s, 1H, 7-NH); LC-MS: *m/z*=393 [M+1]; Anal. calcd. for $C_{20}H_{17}Cl_3N_4O$: C 55.13; H 3.93; N 12.86; Found: C 55.19; H 3.98; N 12.90.

3-(4-Fluorophenyl)-6-(trichloromethyl)-6,7-dihydro-2H-[1,2,4]triazino[2,3-c]quinazolin-2-one (4.3)

Yield: 72.1%; M.p.: 259–261°C; ^{1}H NMR, δ, ppm (*J*, Hz): д 6.45 (d, *J*=4.7, 1H, H-6), 6.87 (t, *J*=7.6, 1H, H-10), 7.04 (d, *J*=8.2, 1H, H-8), 7.20 (t, *J*=8.8, 2H, 3-Ar H-3,5), 7.43 (t, *J*=7.8, 1H, H-9), 8.01 (d, *J*=8.0, 1H, H-11), 8.28 (dd, *J*=8.8, 5.6, 2H, 3-Ar H-2,6), 8.79 (d, *J*=4.8, 1H, 7-NH); LC-MS: m/z=411 [M+1]; Anal. calcd. for $C_{17}H_{10}Cl_3FN_4O$: C 49.60; H 2.45; N 13.61; Found: C 49.63; H 2.49; N 13.64.

General method for synthesis of 3-R-6-(morpholinomethyl)-6,7-dihydro-2H-[1,2,4]ttriazino[2,3-c]quinazoline-2-ones (5.1–5.3)

2 mmol of morpholine (0.286 g) and 2 mmol DIPEA were added to the suspension of 2 mmol of corresponding 6-(chloromethyl)-3-R-6,7-dihydro-2*H*-[1,2,4]triazino[2,3-*c*]quinazoline-2-one (2.1–2.3) in 15 ml dioxane. The formed mixture was refluxed for 10 h. The solvent was evaporated under vacuum, then 20 ml of methanol was added and formed precipitate was filtered. For additional purification, the obtained compounds can be crystallized from methanol.

6-(morpholinomethyl)-3-phenyl-6,7-dihydro-2H-[1,2,4]triazino[2,3-c]quinazolin-2-one (5.1)

Yield 57.4%; M.p.: 205–207°C; ^{1}H NMR, δ, ppm (*J*, Hz): 2.53–2.42 (m, 4H, morpholine H-3,3',5,5'), 2.85–2.67 (m, 2H, –C*H*$_2$–), 3.53–3.42 (m, 4H,), 5.70 (m, 1H, H-6), 6.80 (t, *J*=7.9, 1H, H-10), 6.97 (d, *J*=7.9, 1H, H-8), 7.59–7.20 (m, 6H, 7-NH, H-9, 3-Ar H-3,4,5), 8.01 (d, *J*=7.9, 1H, H-11), 8.21 (d, 2H, *J*=7.6, 3-Ar H-2,6); LC-MS

m/z=376 (M+1); Anal. calcd. for $C_{21}H_{21}N_5O_2$: C 67.18; H 5.64; N 18.65; Found: C 67.22; H 5.69; N 18.69.

3-(4-isopropylphenyl)-6-(morpholinomethyl)-6,7-dihydro-2H-[1,2,4]triazino[2,3-c]quinazolin-2-one (5.2)

Yield 62.3%; M.p.: 197–200°C; ^{1}H NMR, δ, ppm (*J*, Hz): 1.29 (d, *J*=6.8 Hz, 6H, –CH(CH_3)$_2$), 2.48–2.37 (m, 4H, morpholine H-3,3',5,5'), 2.81–2.63 (m, 2H, –CH_2–), 3.01–2.92 (m, 1H, –CH(CH$_3$)$_2$), 3.51–3.36 (m, 4H, morpholine H-2,2',6,6'), 5.63 (m, 1H, H-6), 6.92–6.80 (m, 2H, H-10, 8), 7.28 (d, *J*=8.1 Hz, 2H, 3-Ar H-3,5), 7.43–7.31 (m, 2H, H-9, 7-NH), 7.98 (d, *J*=7.7 Hz, 1H, H-11), 8.09 (d, *J*=8.1 Hz, 2H, 3-Ar H-2,6); LC-MS m/z=418 (M+1); Anal. calcd. for $C_{24}H_{27}N_5O_2$: C 69.04; H 6.52; N 16.77; Found: C 69.09; H 6.59; N 16.84.

3-(4-fluorophenyl)-6-(morpholinomethyl)-6,7-dihydro-2H-[1,2,4]triazino[2,3-c]quinazolin-2-one (5.3)

Yield: 59.7%; M.p.: 208–210°C; ^{1}H NMR, δ, ppm (*J*, Hz): 2.62–2.48 (m, 4H, morpholine H-3,3',5,5'), 2.93–2.74 (m, 2H, –CH$_2$–), 3.58–3.48 (m, 4H, morpholine H-2,2',6,6'), 5.75 (m, 1H, H-6), 6.75 (t, 1H, *J*=7.1, H-10), 6.87 (d, 1H, *J*=7.9, H-8), 7.12 (t, 2H, *J*=7.9, 3-Ar H-3,5 Ar), 7.32 (t, 1H, *J*=7.2, H-9), 7.54 (m, 1H, 7-NH), 8.03 (d, 1H, *J*=7.6, H-11), 8.35 (dd, 2H, 3-Ar H-2,6); LC-MS: m/z=394 [M+1]; Anal. calcd. for $C_{21}H_{20}FN_5O_2$: C 64.11; H 5.12; N 17.80; Found: C 64.09; H 5.08; N 17.85.

General methods for synthesis of 6-(morpholinomethyl)-3-R-2H-[1,2,4]triazino[2,3-c]quinazolin-2-ones (6.1–6.3)

10 mmol (0.87 g) of morpholine was added to the suspension of 2 mmol of corresponding 6-(dichloromethyl)-3-R-6,7-dihydro-2*H*-[1,2,4]-triazino[2,3-*c*]quinazoline-2-one (3.1–3.3) in 15 ml EGEE. The formed mixture was refluxed for 10 hours. After completing of the reaction, the solvent was evaporated under vacuum and 20 ml of methanol was added to the residue. The mixture was stirred and formed precipitate was filtered off. For additional purification, the obtained compounds can be crystallized from methanol.

6-(Morpholinomethyl)-3-phenyl-2H-[1,2,4]triazino[2,3-c]quinazolin-2-one (6.1)

Yield 46.64%; M.p.: 216–218°C; ^{1}H NMR δ, 2.86–2.65 (m, 4H, morpholine H-3,3',5,5'), 3.74–3.56 (m, 4H, morpholine H-2,2',6,6'), 4.12 (s, 2H, CH$_2$), 7.63–7.42 (m, 3H, 3-Ar H-3,4,5), 7.77 (t, *J*=7.2, 1H, H-10), 7.89 (d, *J*=7.8, 1H, H-8), 8.00 (t, *J*=7.6, 1H, H-9), 8.27 (d, *J*=6.8, 2H, 3 Ph H-2,6), 8.63 (d, *J*=7.6, 1H, H-11); LC-MS m/z=374 (M+1); Anal. calcd. for $C_{21}H_{19}N_5O_2$: C 67.55; H 5.13; N 18.76; Found: C 67.61; H 5.09; N 18.81.

3-(4-Isopropylphenyl)-6-(morpholinomethyl)-2H-[1,2,4]triazino[2,3-c]quinazolin-2-one (6.2)

Yield 75.27%; M.p.: 225–227°C; ^{1}H NMR, δ, ppm (*J*, Hz): 1.32 (d, *J*=6.7 Hz, 6H, CH(CH$_3$)$_2$), 2.84–2.64 (m, 4H, morpholine H-3,3',5,5'), 3.03–2.98 (m, 1H, –CH(CH$_3$)$_2$), 3.83–3.64. (m, 4H, morpholine H-2,2',6,6'), 4.10 (s, 2H, CH$_2$), 7.35 (d, *J*=7.8, 2H, 3-Ar H-3,5), 7.73 (t, *J*=7.4, 1H, H-10), 7.86 (d, *J*=7.9, 1H, H-8), 7.96 (t, *J*=7.4, 1H, H-9), 8.20 (d, *J*=7.8, 2H, 3-Ar H-2,6), 8.63 (d, *J*=7.8, 1H, H-11); LC-MS m/z=416 (M+1); Anal. calcd. for $C_{24}H_{25}N_5O_2$: C 69.38; H 6.07; N 16.86; Found: C 69.44; H 6.13; N 16.92.

3-(4-fluorophenyl)-6-(morpholinomethyl)-2H-[1,2,4]triazino[2,3-c]quinazolin-2-one (6.3)

Yield 27.8%; M.p.: 229–231°C; ^{1}H NMR, δ, ppm (*J*, Hz): 2.81–2.66 (m, 4H morpholine H-3,3',5,5'), 3.67–3.40 (m, 4H, morpholine H-2,2',6,6'), 4.11 (s, 2H, CH$_2$), 7.25 (t, *J*=8.3, 2H, 3-Ar H-3,5), 7.74 (t, *J*=7.4, 1H, H-10), 7.86 (d, *J*=8.0, 1H, H-8), 7.97 (t, *J*=7.5, 1H, H-9), 8.45–8.23 (m, 2H, 3-Ar H-2,6), 8.63 (d, *J*=7.9, 1H, H-11); LC-MS m/z=392 (M+1); Anal. calcd. for $C_{21}H_{18}FN_5O_2$: C 64.44; H 4.64; N 17.89; Found: C 64.48; H 4.61; N 17.92.

General methods for synthesis of 3-R-2H-[1,2,4]triazino[2,3-c]quinazioline-2-one (7.1–7.3)

6 mmol of DIPEA (0.78 g) was added to the suspension of 2 mmol of corresponding 6-(trichloromethyl)-3-R-6,7-dihydro-2*H*-[1,2,4]triazino[2,3-*c*]quinazoline-2-one (4.1–4.3) in 15 ml of EGEE. The formed mixture was refluxed for 10 hours. After completing of the reaction, the solvent was evaporated under vacuum and 20 ml of methanol was added to the residue. The mixture was stirred and formed precipitate was filtered off. For additional purification, the obtained compounds can be crystallized from dioxane.

3-Phenyl-2H-[1,2,4]triazino[2,3-c]quinazolin-2-one (7.1)

Yield: 72%; M.p.: 247–249°C; ^{1}H NMR, δ, ppm (*J*, Hz): 7.60 (m, 3H, H-3, H-4', H-5'), 7.85 (t, 1H, *J*=8.0 Hz, H-10), 7.97 (d, 1H, *J*=8.1 Hz, H-8), 8.06 (t, 1H, *J*=8.1, H-9), 8.20 (d, 2H, *J*=8.1 Hz, H-2', H-6'), 8.58 (d, 1H, *J*=8.0 Hz, H-11), 9.10 (s, 1H, H-6); LC-MS: m/z=275 [M+1]; Anal. calcd. for $C_{16}H_{10}N_4O$: C 70.06, H 3.67, N 20.43; Found: C 70.8, H 3.72, N 20.48.

3-(4-(Iso-propyl)phenyl)-2H-[1,2,4]triazino[2,3-c]quinazolin-2-one (7.2)

Yield: 68%; M.p.: 225–227°C; ^{1}H NMR, δ,

ppm (*J*, Hz): 1.29 (d, *J*=6.8 Hz, 6H, −CH(CH_3)$_2$), 3.01 (quin, *J*=6.8 Hz, 1H, −CH(CH_3)$_2$), 7.43 (d, *J*=8.0 Hz, 2H, H-3', H-5'), 7.84 (t, *J*=7.8 Hz, 1H, H-10), 7.96 (d, *J*=7.9 Hz, 1H, H-8), 7.96 (d, *J*=7.9 Hz, 1H, H-8), 8.07 (t, *J*=8.0, 1H, H-9), 8.19 (d, *J*=8.0 Hz, 2H, H-2', H-6'), 8.56 (d, *J*=7.9 Hz, 1H, H-11), 9.08 (s, 1H, H-6); LC-MS, m/z=317 [M+1]; Anal. calcd. For $C_{19}H_{16}N_4O$: C 72.13, H 5.1, N 17.71; Found: C 72.21, H 5.15, N 17.77.

3-(4-Fluorophenyl)-2H-[1,2,4]triazino[2,3-c]quinazolin-2-one (7.3)

Yield: 75%; M.p.: 259−265^{0}C; ^{1}H NMR (DMSO-d_6), δ, ppm (*J*, Hz): 7.36 (t, *J*=8.7 Hz, 2H, H-3', H-5'), 7.71 (t, 1H, *J*=7.8 Hz, H-10), 7.83(d, 1H, *J*=7.9 Hz, H-8), 7.95 (t, 1H, *J*=8.0 Hz, H-9), 8.31 (t, 2H, *J*=8.7 Hz, H-2', H-6'), 8.72 (d, 1H, *J*=8.1 Hz, H-11), 8.87 (s, 1H, H-6); LC-MS, m/z=293 [M+1]; Anal. calcd. for $C_{16}H_9FN_4O$: C 65.75, H 3.1, N 19.17; Found: C 65.83, H 3.13, N 19.25.

REFERENCES

1. *Menezes F.G. Gallardo H., Zucco C.* Recent synthetic applications of trichloro(bromo)methyl containing organic compounds // Quim. Nova. − 2010. − Vol.33. − No. 10. − P.2233-2256.

2. *5,6-Dihydro-[1,2,4]triazolo[1,5-c]quinazolines.* Message 3. Synthesis of 5-trichloromethyl-2-aryl-5,6-dihydro-[1,2,4]-triazolo[1,5-c]quinazolines and features of their reactivity towards N-nucleophiles / Kholodnyak S.V., Voskoboynik O.Yu., Kovalenko S.I., Sergeieva T.Yu., Okovytyy S.I., Shishkina S.V. // J. Org. Pharm. Chem. − 2016. − Vol.14. − No. 2(54). − P.47-52.

3. *Interaction* of 3-(2-aminophenyl)-6-R-1,2,4-triazin-5-ones with acylating reagents: an efficient method for preparation of 6-substituted 3-R-2H-[1,2,4]-triazino[2,3-c]quinazolin-2-ones / Voskoboynik A.Y., Scorina D.Yu., Sergeieva T.Yu., Kovalenko S.I., Okovytyy S.I., Omelchenko I.V., et al. // J. Heterocycl. Chem. − 2016. − Vol.53. − No. 3. − P.776-783.

4. *Voskoboynik O.Yu.* Synthesis, physicochemical properties and anticancer activity of 6-(heterocyclyl-*N*-ylmethyl)-3-R_1-9-R_2-2*H*-[1,2,4]triazino[2,3-*c*]quinazolin-2-ones // Voprosy Khimii i Khimicheskoi Tekhnologii. − 2015. − No. 1. − P.7-12.

5. *Chloromethyl-*, dichloromethyl-, and trichloromethyl-1,2,4-triazines and their 4-oxides: method for the synthesis and tele-substitution reactions with C-nucleophiles / Kozhevnikov D.N., Kataeva N.N., Rusinov V.L., Chupakhin O.N. // Russ. Chem. Bull. − 2004. − Vol.53. − No. 6. − P.1295-1300.

6. *Kelarev V.I., Dibi A., Lunin A.F.* Synthesis and properties of *symm*-triazines. 3. Reactions of 2-alkyl-4,6-bitrichloromethyl-*symm*-triazines containing higher alkyl groups with ammonia and aliphatic amines // Chem. Heterocycl. Compd. − 1985. − Vol.21. − No. 11. − P.1284-1289.

7. *Sym-triazine* derivatives. 9. Reaction of sym-triazines containing trichloromethyl and ethoxycarbonyl groups with phenylhydrazine / Alekseeva N.V., Turchin K.F., Anisimova O.S., Sheinker Yu.N., Yakhontov L.N. // Chem. Heterocycl. Compd. − 1990. − Vol.26. − No. 12. − P.1375-1383.

8. *Nucleophylic* tele-substitution reactions in 3-trichloromethyl-1,2,4-triazines / Kozhevnikov D.N., Kozhevnikov V.N., Rusinov V.L., Chupakhin O.N. // Chem. Heterocycl. Compd. − 1999. − Vol.35. − No. 11. − P.1377-1378.

9. *Hydrazinolysis* of 3-R-[1,2,4]triazino[2,3-*c*]quinazolin-2-ones. Synthetic and theoretical aspects / Sergeieva T.Yu., Voskoboynik O.Yu., Okovytyy S.I., Kovalenko S.I., Shishkina S.V., Shishkin O.V., et al. // J. Phys. Chem. A. − 2014. − Vol.118. − P.1895-1905.

10. *[1,2,4]Triazino[2,3-c]quinazolines* 1. Methods for the preparation and spectral characteristics of substituted 3-R^1-6-R^3-6,7-dihydro-2*H*-[1,2,4]triazino[2,3-c]quinazolin-2-ones / Voskoboynik O.Y., Kolomoets O.S., Kovalenko S.I., Shishkina S.V. // Chem. Heterocycl. Compd. − 2017. − Vol.53. − No. 8. − P.892-904.

11. *[5+1]-Heterocyclisation* in synthesis of as-triazino[2,3-*c*]quinazoline systems / Voskoboynik O.Yu., Karpenko O.V., Sergeieva T.Yu., Kovalenko S.I., Okovyty S.I. // J. Org. Pharm. Chem. − 2013. − Vol.11. − No. 1(41). − P.37-44.

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СИНТЕЗ 6-ХЛОРО-(ДИХЛОРО-, ТРИХЛОРО-)МЕТИЛ-3-R-6,7-ДИГІДРО-2*H*-[1,2,4]ТРИАЗИНО[2,3-*C*]ХІНАЗОЛІН-2-ОНІВ І ЇХ МОДИФІКАЦІЯ В РЕАКЦІЯХ З НУКЛЕОФІЛЬНИМИ ТА НЕНУКОЕОФІЛЬНИМИ ОСНОВАМИ

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В роботі описано синтез 6-хлоро-(дихлоро-, трихлоро)метил-3-R-6,7-дигідро-2*H*-[1,2,4]триазино[2,3-*c*]хіназолін-2-онів та їх модифікацію під дією нуклеофільних та/або основних реагентів. Показано, що 6-хлоро-(дихлоро-, трихлоро)метил-3-R-6,7-дигідро-2*H*-[1,2,4]триазино[2,3-*c*]хіназолін-2-они можуть бути одержані циклоконденсацією 3-(амінофеніл)-6-R-1,2;4-триазин-5(2*H*)-онів з хлоро-(дихлоро-)ацетальдегідом або хлораль гідратом. Додатково була досліджена реакційна здатність синтезованих сполук за відношенням до нуклеофільних і ненуклеофільних основ. Показано, що одержані сполуки під дією морфоліну та/або DIPEA можуть бути перетворені на продукти заміщення, відщеплення або відщеплення з подальшою ізомеризацією та заміщенням. Кип'ятіння 6-(хлорометил)-3-R-6,7-дигідро-2*H*-[1,2,4]триазино[2,3-*c*]хіназолін-2-онів з еквімолярною кількістю морфоліну та 10% надлишком DIPEA в EGEE веде до формування продуктів *N*-алкілування. 6-(Морфолінометил)-3-R-2*H*-[1,2,4]триазино[2,3-*c*]хіназолін-2-они були одержані нагріванням 6-дихлорометил-3-R-6,7-дигідро-2*H*-[1,2,4]триазино[2,3-*c*]хіназолін-2-онів з п'ятикратним надлишком морфоліну в EGEE. Реакція 3-R-6-(трихлорметил)-6,7-дигідро-2*H*-[1,2,4]триазино[2,3-*c*]хіназолін-2-онів з трикратним надлишком DIPEA в EGEE веде до утворення 3-R-2*H*-[1,2,4]триазино[2,3-*c*]хіназолін-2-онів. Були встановлені та обговорені фізико-хімічні

та спектральні характеристики синтезованих сполук.

Ключові слова: 6-R-3-(2-амінофеніл)-1,2,4-триазин-5(2*H*)-они, хлоровані альдегіди та їх гідратні форми, 6-хлоро-(дихлоро-, трихлоро-)метил-3-R-6,7-дигідро-2*H*-[1,2,4]триазино[2,3-*c*]хіназолін-2-они, нуклеофільні та ненуклеофільні основи, синтез.

SYNTHESIS OF 6-CHLORO(DICHLORO-, TRICHLORO-)-METHYL-3-R-6,7-DIHYDRO-2H-[1,2,4]TRIAZINO[2,3-C]QUINAZOLIN-2-ONES AND THEIR MODIFICATION IN REACTIONS WITH NUCLEOPHILIC AND NON-NUCLEOPHILIC BASES

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The synthesis of 6-chloro-(dichloro-, trichloro)methyl-3-R-6,7-dihydro-2H-[1,2,4]triazino[2,3-c]quinazolin-2-ones and their modification under the action of nucleophilic and/or basic reagents are described in this article. It was shown that 6-chloro-(dichloro-, trichloro)methyl-3-R-6,7-dihydro-2H-[1,2,4]triazino-[2,3-c]quinazolin-2-ones can be prepared by cyclocondensation of 3-(aminophenyl)-6-R-1,2;4-triazine-5(2H)-ones with chloro-(dichloro-)acetaldehyde or chloral hydrate. The reactivity of the synthesized compounds toward nucleophilic base morpholine and non-nucleophilic base diisopropylethylamine (DIPEA) under different conditions was studied. It was shown that the prepared compounds under the action of morpholine and/or DIPEA can be converted into the products of substitution, elimination or elimination followed by isomerization and substitution. Refluxing of 6-(chloromethyl)-3-R-6,7-dihydro-2H-[1,2,4]triazino[2,3-c]quinazoline-2-ones with equimolar quantity of morpholine and 10% excess of DIPEA in ethylene glycol monoethyl ether (EGEE) yielded the products on N-alkylation. 6-(Morpholinomethyl)-3-R-2H-[1,2,4]triazino[2,3-c]quinazoline-2-ones were obtained by heating of 6-dichloromethyl-3-R-6,7-dihydro-2H-[1,2,4]triazino[2,3-c]quinazoline-2-ones with five-fold excess of morpholine in EGEE. Reaction of 3-R-6-(trichloromethyl)-6,7-dihydro-2H-[1,2,4]triazino[2,3-c]quinazolin-2-ones with three-fold excess of DIPEA in EGEE yielded 3-R-2H-[1,2,4]triazino[2,3-c]quinazoline-2-ones. The physicochemical and spectral characteristics of the prepared compounds were determined and discussed.

Keywords: 6-R-3-(2-aminophenyl)-1,2,4-triazin-5(2H)-ones; chlorinated aldehydes and their hydrated forms; 6-chloro(dichloro-, trichloro-)-methyl-3-R-6,7-dihydro-2H-[1,2,4]triazino[2,3-c]quinazolin-2-ones; nucleophilic and non-nucleophilic bases; synthesis.

REFERENCES

1. Menezes FG, Gallardo H, Zucco C. Recent synthetic applications of trichloro(bromo)methyl containing organic compounds. *Quim Nova*. 2010; 33(10): 2233-2244. doi: 10.1590/S0100-40422010001000037.

2. Kholodnyak SV, Voskoboynik OY, Kovalenko SI, Sergeieva TY, Okovytyy SI, Shishkina SV. 5,6-Dihydro-[1,2,4]triazolo[1,5-c]quinazolines. Message 3. Synthesis of 5-trichloromethyl-2-aryl-5,6-dihydro-[1,2,4]-triazolo[1,5-*c*]quinazolines and features of their reactivity towards N-nucleophiles. *J Org Pharm Chem*. 2016; 14: 47-52. doi: 10.24959/ophcj.16.879.

3. Voskoboynik AY, Scorina DYu, Sergeieva TYu, Kovalenko SI, Okovytyy SI, Omelchenko IV, et al. Interaction of 3-(2-aminophenyl)-6-R-1,2,4-triazin-5-ones with acylating reagents: an efficient method for preparation of 6-substituted 3-R-2*H*-[1,2,4]-triazino[2,3-*c*]quinazolin-2-ones. *J Heterocycl Chem*. 2016; 53(3): 776-783. doi: 10.1002/jhet.2120.

4. Voskoboynik OYu. Synthesis, physicochemical properties and anticancer activity of 6-(heterocyclyl-N-ylmethyl)-3-R_1-9-R_2-2H-[1,2,4]triazino[2,3-c]quinazolin-2-ones. *Voprosy Khimii i Khimicheskoi Tekhnologii*. 2015; (1): 7-12.

5. Kozhevnikov DN, Kataeva NN, Rusinov VL, Chupakhin ON. Chloromethyl-, dichloromethyl-, and trichloromethyl-1,2,4-triazines and their 4-oxides: method for the synthesis and tele-substitution reactions with C-nucleophiles. *Russ Chem Bull*. 2004; 53: 1295-1300. doi: 10.1023/B:RUCB.0000042289.07168.8f.

6. Kelarev VI, Dibi A, Lunin AF. Synthesis and properties of symm-triazines. 3. Reactions of 2-alkyl-4,6-bistrichloromethyl-symm-triazines containing higher alkyl groups with ammonia and aliphatic amines. *Chem Heterocycl Compd*. 1985; 21: 1284-1289. doi: 10.1007/BF00515231.

7. Alekseeva NV, Turchin KF, Anisimova OS, Sheinker YuN, Yakhontov LN. Sym-triazine derivatives. 9. Reaction of sym-triazines containing trichloromethyl and ethoxycarbonyl groups with phenylhydrazine. *Chem Heterocycl Compd*. 1990; 26: 1375-1383. doi: 10.1007/BF00473967.

8. Kozhevnikov DN, Kozhevnikov VN, Rusinov VL, Chupakhin ON. Nucleophylic tele-substitution reactions in 3-trichloromethyl-1,2,4-triazines. *Chem Heterocycl Compd*. 1999: 35: 1377-1378. doi: 10.1007/BF02252014.

9. Sergeieva TYu, Voskoboynik OYu, Okovytyy SI, Kovalenko SI, Shishkina SV, Shishkin OV, et al. Hydrazinolysis of 3-R-[1,2,4]triazino[2,3-c]quinazolin-2-ones. Synthetic and theoretical aspects. *J Phys Chem A*. 2014; 118: 1895-1905: doi: 10.1021/jp4052616.

10. Voskoboynik OYu, Kolomoets OS, Kovalenko SI, Shishkina SV. [1,2,4]Triazino[2,3-c]quinazolines 1. Methods for the preparation and spectral characteristics of substituted 3-R^1-6-R^3-6,7-dihydro-2*H*-[1,2,4]triazino[2,3-c]quinazolin-2-ones. *Chem Heterocycl Compd*. 2017; 53: 892-904. doi: 10.1007/s10593-017-2142-5.

11. Voskoboynik OYu, Karpenko OV, Sergeieva TYu, Kovalenko SI, Okovyty SI. [5+1]-Heterocyclisation in synthesis of as-triazino[2,3-c]quinazoline systems. *J Org Pharm Chem*. 2013; 1(41): 37-43.