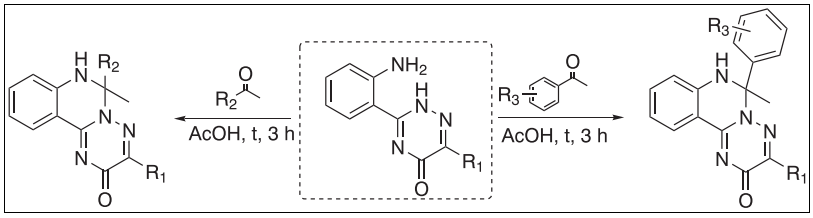
Oleksii Yu. Voskoboynik,[a]* Oleksandra S. Kolomoets,[a] Oleksii M. Antypenko,[a] Galina O. Zhernova,[b] Inna S. Nosulenko,[b] Galyna G. Berest,[a] Volodymyr M. Shvets,[c] and Sergiy I. Kovalenko[a]

[a]Organic and Bioorganic Chemistry Department, Zaporizhzhya State Medical University, 26, Mayakovsky Avenue, Zaporizhzhya 69035, Ukraine
[b]Department of Pharmacognosy, Pharmacology and Botany, Zaporizhzhya State Medical University, 26, Mayakovsky Avenue, Zaporizhzhya 69035, Ukraine
[c]Biochemistry Department, Zaporizhzhya State Medical University, 26, Mayakovsky Avenue, Zaporizhzhya 69035, Ukraine
*E-mail: a.yu.voskoboynik@gmail.com
Received June 27, 2017
DOI 10.1002/jhet.3054
Published online 22 November 2017 in Wiley Online Library (wileyonlinelibrary.com).



Presented article describes the synthesis and hypolipidemic activity of previously unknown 6,6-disubstituted 3-R-6,7-dihydro-2*H*-[1,2,4]triazino[2,3-*c*]quinazolin-2-ones. It was shown, that interaction of 6-R-3-(2-aminophenyl)-1,2,4-triazin-5(2*H*)-ones with methylalkylketones in acetic acid resulted the single product, namely, the desired tricyclic derivatives. At the same time, after refluxing of 6-R-3-(2-aminophenyl)-1,2,4-triazin-5(2*H*)-ones with methylarylketones in acetic acid the mixture of target compound and insignificant amount of corresponding 3-substituted 6-methyl-2*H*-[1,2,4]triazino[2,3-*c*] quinazolin-2-ones were isolated. The mechanism of above-mentioned mixture formation was discussed. The structures of all synthesized compounds were proven using the appropriate physicochemical methods. The compounds with promising lipid-lowering activity were identified and the «structure — hypolipidemic activity» correlations were discussed.

J. Heterocyclic Chem., **55**, 318 (2018).

INTRODUCTION

Disorder of lipid metabolism, which occurs as a result of oxidative stress, is the main factor for the initiation and development of cardiovascular diseases [1–4]. Hyperlipidemia is a major reason of atherosclerosis, coronary heart disease, hypertension, cerebrovascular, and peripheral vascular diseases [5]. Lipid-lowering drugs are commonly used in medical practice to correct these conditions. These include drugs, that reduce levels of triglycerides (TG), total cholesterol, low-density lipoproteins (LDL) and very low-density lipoproteins, and drugs that help to maintain the ability to increase high-density lipoproteins (HDL). The most common lipid-lowering agents that are used in clinical practice can be divided into the following groups: statins, fibrates, the bile acid sequestrants, niacin and its derivatives, derivatives of omega-3 fatty acids, and others (ezetimibe, probucol, benfluorex etc.) [6,7].

It should be noted, that a variety of hyperlipidemias, concomitant diseases, and side effects of these drugs determine the need to create fundamentally new drugs type. So, today aimed search of new lipid-lowering drugs is conducted among various classes of natural and synthetic origin compounds and is associated with a focus of their influence on the molecular mechanisms of hyperlipidemias that participate in this process [7,8]. Great interest in this regard are derivatives of *N*-(aryl-, hetaryl-)alkylamides of anthranilic acid [8,9], spiroimidazoles [10], 5-alkyl-(aryl-)pyrazolo-tetrazoles [11], derivatives of pirazol-3-carboxylic acids [12,13] and their structural analogues [11,14], 5-R-dihydro-pyran[2,3-*d*]pyrimidine-2,4,7-triones [15], substituted of 4-R-aminoquinazolines [16], 2-R-pyrido[2,3-*d*]pyrimidine-4(3*H*)-ones [17], substituted of quinazolin-4(3*H*)-one [18], 3-(4-*i*-propylphenyl)-7-methylpyrazole[1,5-*a*]pyrimidine-6-carbamides [19], and so on.

Versatile mechanisms of hyperlipidemias are known, so as structural diversity of known drugs used for their treatment. Considering this fact, strategy of creation of new drugs may involve the synthesis of compounds with the affinity to the molecular target or an empirical search of substances with lipid-lowering activity with the following establishment of the mechanism of action for aimed chemical modification. Thus, the purpose of this study is to find lipid-lowering drugs among the original

unexplored 6,6-disubstituted 3-R-6,7-dihydro-2*H*-[1,2,4]triazino[2,3-*c*]quinazolin-2-ones, which combine in their structure «pharmacophore» fragment [20,21] and lipophilic aliphatic and aromatic substituents.

RESULTS AND DISCUSSION

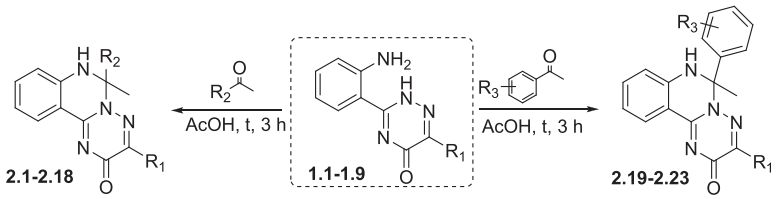
Chemistry. Interaction of 6-R-3-(2-aminophenyl)-1,2,4-triazin-5(2*H*)-ones (**1.1–1.9**) with ketones was used as a method of dihydro[1,2,4]triazine[2,3-*c*]quinazolines formation (Scheme 1). That is, a [5 + 1]-heterocyclization process that led to formation of 6,6-disubstituted 3-R-6,7-dihydro-2*H*-[1,2,4]triazino[2,3-*c*]quinazolin-2-ones (**2.1**–**2.23**). This approach was used for the synthesis of a wide range of compounds **2**, containing at the 6th position aliphatic and aromatic substituents. Refluxing for 3 h in acetic acid was used to obtain compounds **2.1**–**2.18**. The formation of azomethine intermediate, according to the nuclear magnetic resonance (NMR) spectra was not observed, and the yields of final disubstituted reached 60.6–99.2%. Reaction duration was extended up to 6 h to obtain compounds with aromatic ketones **2.19–2.23**, with yields of 24.2–90%. In addition, compounds **2.19–2.23** needed additional purification, as the impurities were 6-methyl-3-R-2*H*-[1,2,4]triazino[2,3-*c*]quinazolin-2-ones, as products of competitive acylation followed by heterocyclization. The above is likely to be explained by steric complications of substituents of aromatic ketones.

The synthesized compounds (**2**) are pale yellow crystals, soluble in dimethylformamide (DMF), sparingly soluble in dioxane and lower alcohols, insoluble in water. Triazino[2,3-*c*]quinazoline fragment in ^{1}H NMR spectra (compounds **2.1–2.23**) had corresponding chemical shifts and multiplicity [22], but H-8 and H-10 protons in some cases (compounds **2.1–2.18**) in the spectrum resonated together as multiplets. Characteristic proton singlets of NH-group (7th position) of compounds **2.1–2.18** in ^{1}H NMR spectra were registered in the range of the 7.17–7.42 ppm. Mentioned proton in spectra of compounds **2.19**–**2.23** was observed at the 7.85–8.47 ppm, due to the deshielding influence of phenyl substituent at the 6th position. In some cases, protons of NH-group and H-9 at the 7th position in the spectrum were observed as multiplets (compounds **2.2**, **2.3**, **2.7**, **2.12**, and **2.17**). In addition, compounds **2.1–2.5** were characterized by proton signals of two methyl groups at the 6th position, which in ^{1}H NMR spectra were registered as equivalent singlets at the 1.67–1.78 ppm, and the methyl group of compounds **2.7–2.23** was found as a singlet at the 2.21–1.66 ppm. A more complex pattern was observed in the spectra of compounds **2.6–2.18** in which methylene protons of ethyl or hexyl residue that were nearby to the 6th position are diastereotopic and appeared as two signals with different multiplicity (doublet of doublets, triplet of doublets, or multiplet) at the 2.96–2.18 ppm and 1.90–1.60 ppm. The above was due to the presence of asymmetric center in the molecule. Classical chemical shifts and multiplicity was character for the substituents at the 3rd position in ^{1}H–NMR spectra [22].

^{13}C NMR spectra also confirmed the structure of the compounds **2.1**, **2.6**, **2.14**, and **2.23**. Such, signals of sp^3-hybridized carbon at the 6th position were observed at the 75.74–78.86 ppm. In addition, corresponding signals of carbon of aliphatic and aromatic groups of the 6th position in the spectra of compound **2.1**, **2.6**, **2.14**, and **2.23** were registered [22].

Ions peaks $[M + 1]^+$ in liquid chromatography mass spectrometry spectra of synthesized compounds **2.1**–**2.23** were recorded, which correspond to the calculated mass. Specific fragmentation of compounds **2.2**, **2.7**, and **2.15** in the mass spectrum (electron ionization) indicate the reaction direction. Thus, these compounds were characterized by the absence (**2.15**) or low-intensive (compounds **2.2** and **2.7**) molecular ion, which was characterized by two alternative fragmentation directions. It is important that direction of fragmentation, charge

Scheme 1. The synthesis of 6,6-disubstituted 3-R-6,7-dihydro-2*H*-[1,2,4]triazino[2,3-*c*]quinazolin-2-ones.



2.1 R_1=Me, R_2=Me; **2.2** R_1=Ph, R_2=Me; **2.3** R_1=4-EtOC_6H_4, R_2=Me; **2.4** R_1=4-FC_6H_4, R_2=Me; **2.5** R_1=thienyl-2, R_2=Me; **2.6** R_1=Me, R_2=Et; **2.7** R_1=Ph, R_2=Et; **2.8** R_1=4-MeC_6H_4, R_2=Et; **2.9** R_1=4-*i*-PrC_6H_4, R_2=Et; **2.10** R_1=3,4-$(Me)_2C_6H_3$, R_2=Et; **2.11** R_1=4-EtOC_6H_4, R_2=Et; **2.12** R_1=4-FC_6H_4, R_2=Et; **2.13** R_1=thienyl-2, R_2=Et; **2.14** R_1=Me, R_2=Hx; **2.15** R_1=Ph, R_2=Hx; **2.16** R_1=4-MeC_6H_4, R_2=Hx; **2.17** R_1=4-FC_6H_4, R_2=Hx; **2.18** R_1=thienyl-2, R_2=Hx; **2.19** R_1=Me, R_3=2-Cl; **2.20** R_1=Me, R_3=4-CN; **2.21** R_1=Ph, R_3=4-CN; **2.22** R_1=Ph, R_3=4-*i*-PrC_6H_4; **2.23** R_1=4-*t*-BuC_6H_4, R_3=4-ClC_6H_4.

delocalization, and intensity of the ion in the spectrum were determined by the electron-donor effect of substituent at the 6th position. The first direction was associated with cleavage of C-C bond at the 6th position of alkyl moiety and formation of F_1 ($[M\text{-}Alk]^+$) with m/z 290 (4.0–50.1%). Second direction was the cleavage of bonds C(2) – C(3) and N(4) – N(5) and formation of F_2 ($[C_6H_5CH = N]^+$) with m/z 103 (8.0–100%). F_1 undergo additional fragmentation through rupture of bonds C(2) – C(3) and N(4) – N(5) and the formation of ions with m/z 187/186 (8.8–100%). High-intensity ion peaks $[C_3H_5]^+$ (*m/z* 41, 48.8%), $[C_3H_7]^+$ (*m/z* 43, 97.2%), $[C_4H_7]^+$ (*m/z* 55, 34.6%), $[C_4H_9]^+$ (m/z 57, 8.1%) are an interesting aspect of the mass spectrum of compound **2.15**, which characterized hexyl moiety at the 6th position [23].

Pharmacology. The mechanism of hyperlipidemic action of ergocalciferol oil solution and surfactant «Tween-80» is associated with inhibition of lipoprotein lipase [24,25]. This fact caused inhibition of TG hydrolysis and led to a rapid increase of TG and LDL concentration in plasma. During the experiment, it was established (Table 1) that the level of Triglycerides (TL), TG, and LDL increased compared to the intact group of animals by 33%, 158%, and 148% respectively. Cholesterol did not differ from that in group of intact animals. The concentration of HDL decreased by 77%, and atherogenic factor increased per 7.8 times.

Compounds **2.1**, **2.6**, **2.14**, **2.15**, and **2.20** were chosen for preliminary screening for hypolipidemic activity. The choice of the above-mentioned compounds was dictated by different nature of substituents in positions three and six and allowed estimation of «structure – hypolipidemic activity» relationships.

Administration of the studied compounds to animals with experimental pathology cause the decrease of lipid metabolism parameters (TL cholesterol, TG, and LDL), while at the same time, level of antiatherogenic HDL fraction was increased (Table 1). Conducted structure - activity relationship analysis showed that the nature of the substituent at the 6th position significantly affected the hypolipidemic activity. Namely, activity increased in the following sequence: 4-cyanophenyl (**2.20**) < methyl (**2.1**) < ethyl (**2.6**) < hexyl (**2.14**, **2.15**) which is logical, considering to lipophilicity of the substituent. It is important that the replacement of the methyl group (**2.14**) at the 3rd position by phenyl (**2.15**) also led to a reduction of activity.

The most active compound, namely 6-hexyl-3,6-dimethyl-6,7-dihydro-2*H*[1,2,4]triazine[2,3-*c*]quinazolin-2-one (**2.14**) decreased the level of TL by 54%, 65%, and 35% compared to intact, control group, and group of rats whom nicotinic acid was administered, respectively (Table 1). The level of cholesterol was also decreased by 48% after administration of the compound **2.14** compared with intact, 46% compared with the control group, and 43% in comparison with the group of rats whom nicotinic acid was administered. In addition, the tendency to reduce TG level was observed, by 47% compared with intact, 80% compared with the control group, and 75% in comparison with the group of rats whom nicotinic acid was administered.

After the introduction of compound **2.14** the concentration of LDL – a class of blood lipoproteins, which are the most atherogenic, decreased by 4% compared with intact, by 61% compared with the control group, and by 55% in comparison with the group of rats whom nicotinic acid was administered. Level of HDL that exhibit antiatherogenic properties was reduced by 57% compared with intact, and HDL was increased by 85% and 17% compared with control and rats, who receive nicotinic acid. Estimated risk of atherosclerosis, atherogenic factor, after the administration of compound **2.14** was 43% higher than such intact group had, 82% lower than in the control and 66% lower compared with rats whom nicotinic acid was administered.

Therefore, a preliminary screening of lipid-lowering activity of 6-disubstituted 3-R-6,7-dihydro-2*H*-[1,2,4] triazino[2,3-*c*]quinazolin-2-ones revealed a number of promising compounds that compete activity or exceed the reference drug – nicotinic acid. Compound **2.14**, which effectively reduced the level of TL, cholesterol, TG,

Table 1

The lipid-lowering activity results of the synthesized compounds.

The experimental group of animals	TL, g/L	Cholesterol, mmol/L	TG, mmol/L	HDL, mmol/L	LDL, mmol/L	Atherogenic coefficient
Intact	5.732 ± 0.154	2.083 ± 0.310	0.910 ± 0.510	1.133 ± 0.240	0.511 ± 0.130	0.84 ± 0.04
Control	7.639 ± 0.258	2.003 ± 0.033	2.351 ± 0.045	0.265 ± 0.018	1.268 ± 0.180	6.56 ± 0.06
2.1	5.319 ± 0.100	1.888 ± 0.062	1.342 ± 0.077	0.427 ± 0.150	0.851 ± 0.150	3.42 ± 0.05
2.6	4.076 ± 0.115	1.231 ± 0.033	0.424 ± 0.051	0.349 ± 0.170	0.692 ± 0.140	2.52 ± 0.06
2.14	2.656 ± 0.159	1.077 ± 0.095	0.481 ± 0.053	0.489 ± 0.014	0.492 ± 0.120	1.20 ± 0.04
2.15	5.329 ± 0.113	1.235 ± 0.046	1.631 ± 0.079	0.271 ± 0.160	0.224 ± 0.110	3.56 ± 0.07
2.20	5.380 ± 0.100	1.910 ± 0.062	1.356 ± 0.077	0.430 ± 0.150	0.863 ± 0.150	3.44 ± 0.05
Nicotinic acid	4.118 ± 0.030	1.890 ± 0.021	1.907 ± 0.057	0.417 ± 0.017	1.092 ± 0.160	3.53 ± 0.07

TG, triglycerides; HDL, high-density lipoproteins; LDL, low-density lipoproteins.

LDL, and at the same time increased HDL in conditions of induced hyperlipidemia is promising. It requires further research to study the mechanism of action for possible usage in the prevention and treatment of atherosclerotic cardiovascular-circulatory diseases.

EXPERIMENTAL

Chemistry. ***General Methods.*** Melting points were determined in open capillary tubes and were uncorrected. The elemental analyses (C, H, N, and 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. Infrared spectra (4,000–600 cm^{-1}) were recorded on a Bruker ALPHA FT-IR spectrometer (Bruker Bioscience, Germany) using a module for measuring attenuated total reflection. ^1H NMR spectra (400 MHz) and ^{13}C NMR spectra (100 MHz) were recorded on Varian-Mercury 400 (Varian Inc., Palo Alto, CA, USA) spectrometers with tetramethylsilane as internal standard in DMSO-d_6 solution. Liquid chromatography–mass spectrocopy were recorded using chromatography/mass spectrometric system that consists of high-performance liquid chromatograph «Agilent 1100 Series» (Agilent, Palo Alto, CA, USA) equipped with diode-matrix and mass-selective detector «Agilent LC/MSD SL» (atmospheric pressure chemical ionization). Electron impact mass spectra (EI-MS) were recorded on a Varian 1,200 L instrument at 70 eV (Varian, USA).

Compounds **1.1–1.9** were obtained according to the described synthetic protocols [26]. The other starting reagents and solvents were obtained from commercially available sources and were used without additional purification.

General Procedure for the Synthesis of 6,6-Disubstituted 3-R-6,7-Dihydro-2H-[1,2,4]Triazino[2,3-c]Quinazolin-2-Ones (2.1–2.23). To a suspension of 10 mmol of corresponding 6-R-3-(2-aminophenyl)-1,2,4-triazin-5(2*H*)-ones (**1.1–1.9**) in 20 ml of glacial acetic acid 10 mmol of the appropriate ketones (propan-2-one, butan-2-one, octan-2-one, 1-(2-chlorophenyl)ethan-1-one, 1-(4-*i*-propylphenyl)ethan-1-one, 1-(4-chlorophenyl)ethan-1-one, 4-acetylbenzonitrile) was added. Mixture was refluxed for 3–6 h and cooled. The formed precipitate was filtered and dried. If necessary, it was crystallized with acetic acid.

3,6,6-Trimethyl-6,7-dihydro-2H-[1,2,4]triazino[2,3-c] quinazolin-2-one (2.1). Yield: 2.0 g (81.1%). White-yellow crystals. mp 271–273°C. IR (ν, cm^{-1}): 3265, 3019, 2882, 2830, 1724, 1635, 1612, 1593, 1521, 1485, 1417, 1387, 1370, 1335, 1271, 1215, 1198, 1158, 1144, 1107, 1032, 1009, 986, 958, 949, 911, 863, 828, 771, 754, 691, 663, 635. ^1H NMR, δ, ppm (*J*, Hz): 7.95 (d, 1H, *J* = 7.5 Hz, H-11), 7.35 (t, 1H, *J* = 7.5 Hz, H-9), 7.30 (s, 1H, NH), 6.81 (m, 2H, H-8, 10), 2.23 (s, 3H, 3-CH_3), 1.67 (s, 6H, 6-$(CH_3)_2$). ^{13}C NMR, δ, ppm: 161.58, 152.42, 150.92, 144.75, 134.16, 126.66, 117.96, 114.86, 112.38, 95.49, 75.74, 26.10, 17.24. LC–MS, *m/z* = 243 $[M + 1]^+$. Anal. Calcd. for $C_{13}H_{14}N_4O$: C, 64.45; H, 5.82; N, 23.13. Found: C, 64.51; H, 5.89; N, 23.19.

*6,6-Dimethyl-3-phenyl-6,7-dihydro-2H-[1,2,4] triazino[2,3-c]quinazolin-2-one (**2.2**).* Yield: 2.8 g (93.0%). White-yellow crystals. mp 291–292°C. ^1H NMR, δ, ppm (*J*, Hz): 8.18 (d, 2H, *J* = 8.0 Hz, H-2,6 Ph), 8.00 (d, 1H, *J* = 7.8 Hz, H-11), 7.54–7.20 (m, 5H, H-9, NH, H-3, 4, 5 Ph), 6.84 (m, 2H, H-8, 10), 1.78 (s, 6H, 6-$(CH_3)_2$). EI-MS, *m/z* (I_{rel}, %): 305 (1.1), 290 (5.5), 188 (8.8), 187 (100), 159 (5.2), 146 (5.9), 145 (16.1), 144 (78.9), 143 (7.8), 119 (18), 118 (29.6), 117 (45.1), 116 (25.1), 104 (13.2), 103 (48.3), 92 (13.4), 91 (22), 90 (56.4), 89 (41.8), 88 (10), 86 (7.6), 85 (6.8), 83 (9.3), 82 (5.6), 81 (5), 79 (5.1), 78 (8.6), 77 (57.5), 76 (94.3), 75 (16.6), 71 (7.7), 69 (12.8), 66 (7.4), 65 (13.7), 64 (13.8), 63 (41), 62 (12.4), 60 (6.1), 57 (24), 56 (17.7), 55 (17.3), 53 (6.3), 52 (21.9), 51 (40.8), 50 (30.7), 49 (15.6), 45 (7.9), 43 (12.1), 42 (12.9), 41 (15). LC–MS, *m/z* = 305 $[M + 1]^+$. Anal. Calcd. for $C_{18}H_{16}N_4O$: C, 71.04; H, 5.30; N, 18.41. Found: C, 71.11; H, 5.39; N, 18.49.

*3-(4-Ethoxyphenyl)-6,6-dimethyl-6,7-dihydro-2H-[1,2,4] triazino[2,3-c]quinazolin-2-one (**2.3**).* Yield: 3.1 g (88.8%). White-yellow crystals. mp 262–263°C. ^1H NMR, δ, ppm (*J*, Hz): 8.22 (d, 2H, *J* = 8.4 Hz, H-2, 6 Ph), 7.99 (d, 1H, *J* = 7.8 Hz, H-11), 7.42–7.28 (m, 2H, H-9, NH), 6.94 (d, 2H, *J* = 8.4 Hz, H-3, 5 Ph), 6.88–6.69 (m, 2H, *J* = 7.1 Hz, H-8, 10), 4.11 (dd, 2H, *J* = 13.2, 6.4 Hz, $-OC\underline{H_2}CH_3$), 1.77 (s, 6H, 6-$(CH_3)_2$), 1.43 (t, 3H, *J* = 6.7 Hz, $-OCH_2C\underline{H_3}$). LC–MS, *m/z* = 349 $[M + 1]^+$. Anal. Calcd. for $C_{20}H_{20}N_4O_2$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.99; H, 5.81; N, 16.11.

*3-(4-Fluorophenyl)-6,6-dimethyl-6,7-dihydro-2H-[1,2,4] triazino[2,3-c]quinazolin-2-one (**2.4**).* Yield: 2.6 g (81.5%). White-yellow crystals. mp 268–270°C. ^1H NMR, δ, ppm (*J*, Hz): 8.29 (t, 2H, H-2, 6 Ph), 7.99 (d, 1H, *J* = 7.6 Hz, H-11), 7.42 (s, 1H, NH), 7.39 (t, 1H, H-9), 7.21 (t, 2H, *J* = 8.4 Hz, H-3,5 Ph), 6.88–6.71 (m, 2H, H-8, 10), 1.77 (s, 6H, 6-$(CH_3)_2$). LC–MS, *m/z* = 323 $[M + 1]^+$. Anal. Calcd. for $C_{18}H_{15}FN_4O$: C, 67.07; H, 4.69; N, 17.38. Found: C, 67.13; H, 4.74; N, 17.42.

*6,6-Dimethyl-3-(thiophen-2-yl)-6,7-dihydro-2H-[1,2,4] triazino[2,3-c]quinazolin-2-one (**2.5**).* Yield: 3.1 g (98.4%). White-yellow crystals. mp 277–278°C. ^1H NMR, δ, ppm (*J*, Hz): 8.23 (s, 1H, H-3 thiophene), 7.99 (d, 1H, *J* = 7.6 Hz, H-11), 7.67 (d, 1H, *J* = 4.4 Hz, H-5

thiophene), 7.42 (s, 1H, NH), 7.38 (t, 1H, *J* = 7.6 Hz, H-9), 7.17 (t, 1H, H-4 thiophene), 6.84 (m, 2H, H-8, 10), 1.77 (s, 6H, $-(CH_3)_2$). LC–MS, *m/z* = 311 $[M + 1]^+$. Anal. Calcd. for $C_{16}H_{14}N_4OS$: C, 61.92; H, 4.55; N, 18.05. Found: C, 62.01; H, 4.60; N, 18.11.

6-Ethyl-3,6-dimethyl-6,7-dihydro-2H-[1,2,4]triazino[2,3-c]quinazolin-2-one ***(2.6)****.* Yield: 1.85 g (87.3%). White-yellow crystals. mp 268–269°C. ^{1}H NMR, δ, ppm (*J*, Hz): 7.93 (d, 1H, *J* = 7.7 Hz, H-11), 7.30 (t, 1H, *J* = 7.5 Hz, H-9), 7.18 (s, 1H, NH), 6.82–6.71 (m, 2H, H-8, 10), 2.22 (s, 3H, 3-CH_3), 2.18 (dd, 1H, *J* = 14.0, 7.1 Hz, $-C\underline{H_2}CH_3$), 1.79 (dd, 1H, *J* = 14.0, 7.1 Hz, 1H, $-CH_2C\underline{H_3}$), 1.66 (s, 3H, 6-CH_3), 0.92 (t, 3H, *J* = 7.0 Hz, $-CH_2C\underline{H_3}$). ^{13}C NMR, δ, ppm: 161.40, 152.86, 150.83, 144.86, 134.05, 126.69, 117.60, 114.56, 111.99, 78.35, 31.16, 24.68, 17.21, 7.74. LC–MS, *m/z* = 256 $[M + 1]^+$. Anal. Calcd. for $C_{14}H_{16}N_4O$: C, 65.61; H, 6.29; N, 21.86. Found: C, 65.69; H, 6.34; N, 21.89.

6-Ethyl-6-methyl-3-phenyl-6,7-dihydro-2H-[1,2,4]triazino[2,3-c]quinazolin-2-one ***(2.7)****.* Yield: 2.5 g (80.0%). White-yellow crystals. mp 230–231°C. ^{1}H NMR, δ, ppm (*J*, Hz): 8.18 (d, 2H, *J* = 8.0 Hz, H-2, 6 Ph), 7.99 (d, 1H, *J* = 7.6 Hz, H-11), 7.49–7.36 (m, 3H, H-3, 4, 5 Ph), 7.39–7.20 (m, 2H, NH, H-9), 6.80 (m, 2H, H-8, 10), 2.29 (dd, 1H, *J* = 14.0, 7.0 Hz, $-C\underline{H_2}CH_3$), 1.89 (dd, 1H, *J* = 13.7, 7.1 Hz, $\underline{CH_2}CH_3$), 1.77 (s, 3H, 6-CH_3), 0.98 (t, 3H, *J* = 6.9 Hz, $CH_2\underline{CH_3}$). EI-MS, *m/z* (I_{rel}, %): 318 (2.9), 290 (50.1), 200 (10.1), 187 (14.4), 186 (100), 158 (5.9), 143 (9.3), 103 (8), 102 (6.7), 77 (7.9), 76 (14.5). LC–MS, *m/z* = 319 $[M + 1]^+$. Anal. Calcd. for $C_{19}H_{18}N_4O$: C, 71.68; H, 5.70; N, 17.60. Found: C, 71.74; H, 5.67; N, 17.66.

6-Ethyl-6-methyl-3-(4-methylphenyl)-6,7-dihydro-2H-[1,2,4]triazino[2,3-c]quinazolin-2-one ***(2.8)****.* Yield: 3.1 g (91.9%). White-yellow crystals. mp 263–266°C. ^{1}H NMR, δ, ppm (*J*, Hz): 8.09 (d, 2H, *J* = 7.3 Hz, H-2, 6 Ph), 7.98 (d, 1H, *J* = 7.6 Hz, H-11), 7.33 (t, 1H, H-9), 7.28 (s, 1H, NH), 7.22 (d, 2H, *J* = 7.4 Hz, H-3, 5 Ph), 6.88–6.68 (m, 2H, H-8, H-10), 2.42 (s, 3H, CH_3), 2.28 (dd, 1H, *J* = 13.7, 6.9 Hz, $-C\underline{H_2}CH_3$), 1.89 (dd, 1H, *J* = 13.8, 6.8 Hz, $-C\underline{H_2}CH_3$), 1.76 (s, 3H, 6-CH_3), 0.98 (t, 3H, *J* = 6.4 Hz, $-CH_2C\underline{H_3}$). LC–MS, *m/z* = 333 $[M + 1]^+$. Anal. Calcd. for $C_{20}H_{20}N_4O$: C, 72.27; H, 6.06; N, 16.86. Found: C, 72.31; H, 6.14; N, 16.91.

6-Ethyl-3-(4-i-propylphenyl)-6-methyl-6,7-dihydro-2H-[1,2,4]triazino[2,3-c]quinazolin-2-one ***(2.9)****.* Yield: 2.6 g (71.7%). White-yellow crystals. mp 268–269°C. ^{1}H NMR, δ, ppm (*J*, Hz): 8.10 (d, 1H, *J* = 7.9 Hz, H-2, 6 Ph), 7.98 (d, 1H, *J* = 7.7 Hz, H-11), 7.33 (t, 1H, H-9), 7.29 (d, 3H, NH, H-3, 5 Ph), 6.92–6.63 (m, 2H, H- 8, 10), 2.96 (dd, 1H, *J* = 13.6, 6.8 Hz, 1H, $-C\underline{H}(CH_3)_2$), 2.28 (dd, 1H, *J* = 13.3, 6.7 Hz, $-C\underline{H_2}CH_3$), 1.90 (dd, 1H, *J* = 13.7, 6.6 Hz, $-C\underline{H_2}CH_3$), 1.76 (s, 3H, 6-CH_3), 1.29 (d, 6H, *J* = 6.7 Hz, $-CH(C\underline{H_3})_2$), 0.98 (t, 3H, *J* = 7.0 Hz, $-CH_2C\underline{H_3}$). LC–MS, *m/z* = 361 $[M + 1]^+$. Anal. Calcd. for $C_{22}H_{24}N_4O$: C, 73.31; H, 6.71; N, 15.54. Found: C, 73.38; H, 6.79; N, 15.59.

3-(3,4-Dimethylphenyl)-6-ethyl-6-methyl-6,7-dihydro-2H-[1,2,4]triazino[2,3-c]quinazolin-2-one ***(2.10)****.* Yield: 3.4 g (86.1%). White-yellow crystals. mp 268–269°C. ^{1}H NMR, δ, ppm (*J*, Hz): 7.98 (d, 1H, *J* = 7.8 Hz, H-11), 7.94 (s, 1H H-2 Ph), 7.88 (d, 1H, *J* = 7.8 Hz, H-6 Ph), 7.33 (t, 1H, *J* = 7.5 Hz, H-9), 7.27 (s, 1H, NH), 7.16 (d, 1H, *J* = 7.7 Hz, H-5 Ph), 6.88–6.71 (m, 2H, H-8, 10), 2.34 (s, 3H, 4-CH_3), 2.32 (s, 3H, 3-CH_3), 2.30–2.20 (dd, 1H, *J* = 14.0, 6.8 Hz, $-C\underline{H_2}CH_3$), 1.89 (dd, 1H, *J* = 14.0, 6.8 Hz, $-C\underline{H_2}CH_3$), 1.76 (s, 3H, 6-CH_3), 0.98 (t, 3H, *J* = 6.9 Hz, $-CH_2C\underline{H_3}$). LC–MS, *m/z* = 347 $[M + 1]^+$. Anal. Calcd. for $C_{21}H_{22}N_4O$: C, 72.81; H, 6.40; N, 16.17. Found: C, 72.86; H, 6.46; N, 16.23.

3-(4-Ethoxyphenyl)-6-ethyl-6-methyl-6,7-dihydro-2H-[1,2,4]triazino[2,3-c]quinazolin-2-one ***(2.11)****.* Yield: 3.6 g (99.2%). White-yellow crystals. mp 235–238°C. ^{1}H NMR, δ, ppm (*J*, Hz): 8.20 (d, 2H, *J* = 8.0 Hz, H-2, 6 Ph), 7.97 (d, 1H, *J* = 7.7 Hz, H-11), 7.32 (t, 1H, *J* = 7.4 Hz, H-9), 7.26 (s, 1H, NH), 6.91 (d, 2H, *J* = 8.0 Hz, H-3, 5 Ph), 6.86–6.70 (m, 2H, H-8, 10), 4.10 (dd, 2H, *J* = 12.9, 6.2 Hz, $-OC\underline{H_2}CH_3$), 2.28 (dd, 1H, *J* = 14.1, 7.0 Hz, $-C\underline{H_2}CH_3$), 1.87 (dd, 1H, *J* = 14.1, 7.0 Hz, $-C\underline{H_2}CH_3$), 1.76 (s, 3H, 6-CH_3), 1.43 (t, 3H, *J* = 6.3 Hz, $-OCH_2C\underline{H_3}$), 0.98 (t, 3H, *J* = 6.7 Hz, $-CH_2C\underline{H_3}$). LC–MS, *m/z* = 363 $[M + 1]^+$. Anal. Calcd. for $C_{21}H_{22}N_4O_2$: C, 69.59; H, 6.12; N, 15.46. Found: C, 69.62; H, 6.18; N, 15.51.

6-Ethyl-3-(4-fluorophenyl)-6-methyl-6,7-dihydro-2H-[1,2,4]triazino[2,3-c]quinazolin-2-one ***(2.12)****.* Yield: 2.4 g (39.8%). White-yellow crystals. mp 200–202°C. ^{1}H NMR, δ, ppm (*J*, Hz): 8.34–8.20 (m, 2H, H-2, 6 Ph), 7.98 (d, 1H, *J* = 7.8 Hz, H-11), 7.33 (m, 2H, NH, H-9), 7.16 (t, 2H, *J* = 8.1 Hz, H-3, 5 Ph), 6.86–6.70 (m, 2H, H-8, H-10), 2.28 (dd, 1H, *J* = 13.1, 6.5 Hz, $-C\underline{H_2}CH_3$), 1.89 (dd, 1H, *J* = 13.7, 6.3 Hz, $-C\underline{H_2}CH_3$), 1.76 (s, 1H, 6-CH_3), 0.97 (t, 3H, *J* = 6.8 Hz, 1H, $-CH_2C\underline{H_3}$). LC–MS, *m/z* = 337 $[M + 1]^+$. Anal. Calcd. for $C_{19}H_{17}FN_4O$: C, 67.84; H, 5.09; N, 16.66. Found: C, 67.80; H, 5.03; N, 16.59.

6-Ethyl-6-methyl-3-(thiophen-2-yl)-6,7-dihydro-2H-[1,2,4]triazino[2,3-c]quinazolin-2-one ***(2.13)****.* Yield: 2.8 g (86.6%). White-yellow crystals. mp 246–247°C. ^{1}H NMR, δ, ppm (*J*, Hz): 8.22 (d, 1H, *J* = 2.1 Hz, H-3

thiophene), 7.98 (d, 1H, *J* = 7.7 Hz, H-11), 7.59 (d, 1H, *J* = 4.5 Hz, H-5 thiophene), 7.32 (m, 2H, H-9, NH), 7.14 (t, 1H, H-4 thiophene), 6.80 (m, 2H, H-8, H-10), 2.28 (dd, 1H, *J* = 14.0, 7.1 Hz, $-C\underline{H_2}CH_3$), 1.88 (dd, 1H, *J* = 14.0, 7.1 Hz, $-C\underline{H_2}CH_3$), 1.76 (s, 3H, 6-CH_3), 0.97 (t, 3H, *J* = 6.9 Hz, $-CH_2C\underline{H_3}$). LC–MS, *m/z* = 325 $[M + 1]^+$. Anal. Calcd. for $C_{17}H_{16}N_4OS$: C, 62.94; H, 4.97; N, 17.27. Found: C, 63.02; H, 5.02; N, 17.31.

6-Hexyl-3,6-dimethyl-6,7-dihydro-2H-[1,2,4]triazino[2,3-c]quinazolin-2-one ***(2.14)****.* Yield: 1.4 g (44.9%). White-yellow crystals. mp 143–147°C. ^{1}H NMR, δ, ppm (*J*, Hz): 7.93 (d, 1H, *J* = 7.5 Hz, H-11), 7.29 (t, 1H, *J* = 6.9 Hz, 1H, H-9), 7.17 (s, 1H, NH), 6.84–6.69 (m, 2H, H-8, 10), 2.21 (s, 3H, $-CH_3$), 2.18–2.01 (m, 1H, $-C\underline{H_2}(CH_2)_4CH_3$), 1.85–1.60 (m, 4H, $-C\underline{H_2}(CH_2)_4CH_3$, 6-$C\underline{H_3}$), 1.44–1.08 (m, 8H,-$CH_2(C\underline{H_2})_4CH_3$), 0.85 (t, 3H, $-\underline{CH_3}$). ^{13}C NMR, δ, ppm: 152.76, 150.82, 144.81, 134.19, 126.67, 126.66, 117.61, 114.56, 111.93, 99.41, 78.05, 38.12, 30.96, 28.54, 25.04, 22.73, 21.93, 17.24, 13.71. LC–MS, *m/z* = 313 $[M + 1]^+$. Anal. Calcd. for $C_{18}H_{24}N_4O$: C, 69.20; H, 7.74; N, 17.93. Found: 69.25; H, 7.80; N, 17.97.

6-Hexyl-6-methyl-3-phenyl-6,7-dihydro-2H-[1,2,4]triazino[2,3-c]quinazolin-2-one ***(2.15)****.* Yield: 2.3 g (60.6%). White-yellow crystals. mp 169–190°C. ^{1}H NMR, δ, ppm (*J*, Hz): 8.17 (d, 2H, *J* = 6.9 Hz, H-2, 6 Ph), 7.99 (d, 1H, *J* = 7.7 Hz, H-11), 7.53–7.38 (m, 3H, H-3, 4, 5 Ph), 7.34 (t, 1H, *J* = 7.6 Hz, H-9), 7.29 (s, 1H, NH), 6.89–6.67 (m, 2H, H-8, 10), 2.23 (td, 1H, *J* = 12.5 Hz, $-C\underline{H_2}(CH_2)_4CH_3$), 1.83 (td, 1H, *J* = 12.5 Hz, $-C\underline{H_2}(CH_2)_4CH_3$), 1.76 (s, 3H, 6-$CH_3$), 1.51–1.32 (m, 2H, $-CH_2C\underline{H_2}(CH_2)_3CH_3$), 1.24 (s, 6H, $-CH_2CH_2(C\underline{H_2})_3CH_3$), 0.84 (t, 3H, $-(CH_2)_5C\underline{H_3}$). EI-MS, *m/z* ($I_{rel}$, %): 290 (4.0), 189 (6.3), 188 (14.5), 187 (93.5), 186 (10.7), 161 (7.4), 160 (12.8), 159 (6.8), 146 (9.2), 145 (9.6), 144 (41.5), 143 (5), 129 (10.9), 119 (5.8), 118 (25.9), 117 (27.1), 116 (17.8), 105 (6.2), 104 (34.2), 103 (100), 102 (28.8), 91 (8.4), 90 (19.7), 89 (15.8), 86 (5.6), 84 (8.3), 77 (41.2), 76 (52.4), 75 (16.4), 69 (5.3), 65 (9), 64 (8.8), 63 (34.3), 57 (8.1), 56 (17), 55 (34.6), 53 (7.7), 51 (10.4), 50 (5.5), 43 (97.2), 42 (27.5), 41 (48.8). LC–MS, *m/z* = 375 $[M + 1]^+$. Anal Calcd. for $C_{23}H_{26}N_4O$: C, 73.77; H, 7.00; N, 14.96. Found: C, 73.80; H, 7.04; N, 15.01.

6-Hexyl-6-methyl-3-(4-methylphenyl)-6,7-dihydro-2H-[1,2,4]triazino[2,3-c]quinazolin-2-one ***(2.16)****.* Yield: 2.6 g (67.9%). White-yellow crystals. mp 173–174°C. ^{1}H NMR, δ, ppm (*J*, Hz): 8.09 (d, 2H, *J* = 7.7 Hz, H-2, 6 Ph), 7.98 (d, 1H, *J* = 7.7 Hz, H-11), 7.33 (t, 1H, *J* = 7.5 Hz, H-9), 7.27 (s, 1H, NH), 7.22 (d, 2H, *J* = 7.7 Hz, 2H, H-3, 5 Ph), 6.88–6.70 (m, 2H, H-8, 10), 2.42 (s, 3H, $-CH_3$), 2.23 (m, 1H, $-C\underline{H_2}(CH_2)_4CH_3$), 1.87–1.77 (m, 1H, $-C\underline{H_2}(CH_2)_4CH_3$), 1.75 (s, 1H, 6-$CH_3$), 1.48–1.31 (m, 2H, $-CH_2C\underline{H_2}(CH_2)_3CH_3$), 1.24 (m, 3H, $-CH_2CH_2(C\underline{H_2})_3CH_3$), 0.84 (t, 3H, $-(CH_2)_5C\underline{H_3}$). LC–MS, *m/z* = 389 $[M + 1]^+$. Anal Calcd. for $C_{24}H_{28}N_4O$: C, 74.20; H, 7.26; N, 14.42. Found: C, 74.26; H, 7.30; N, 14.45.

3-(4-Fluorophenyl)-6-hexyl-6-methyl-6,7-dihydro-2H-[1,2,4]triazino[2,3-c]quinazolin-2-one ***(2.17)****.* Yield: 2.4 g (61.1%). White-yellow crystals. mp 268–269°C. ^{1}H NMR, δ, ppm (*J*, Hz): 8.34–8.18 (m, 2H, H-2, 6 Ph), 7.98 (d, 1H, *J* = 1.1 Hz, H-11), 7.41–7.22 (m, 2H, H-9, NH), 7.16 (t, 2H, *J* = 8.2 Hz, H-3, 5 Ph), 6.88–6.71 (m, 2H, H-8, 10), 2.21 (td, 1H, *J* = 12.3 Hz, $-C\underline{H_2}(CH_2)_4CH_3$), 1.82 (td, 1H, *J* = 12.3 Hz, $-C\underline{H_2}(CH_2)_4CH_3$), 1.76 (s, 3H, 6-$CH_3$), 1.51–1.32 (m, 2H, $-CH_2C\underline{H_2}(CH_2)_3CH_3$), 1.24 (s, 6H, $-CH_2CH_2(C\underline{H_2})_3CH_3$), 0.83 (s, 3H, $-(CH_2)_5C\underline{H_3}$). LC–MS, *m/z* = 393 $[M + 1]^+$. Anal Calcd. for $C_{23}H_{25}FN_4O$: C, 70.39; H, 6.42; N, 14.28. Found: C, 70.43; 6.47; N, 14.32.

6-Hexyl-6-methyl-3-(thiophen-2-yl)-6,7-dihydro-2H-[1,2,4]triazino[2,3-c]quinazolin-2-one ***(2.18)****.* Yield: 3.0 g (79.6%). White-yellow crystals. mp 170–172°C. ^{1}H NMR, δ, ppm (*J*, Hz): 8.22 (s, 1H, H-3 thiophene), 7.98 (d, 1H, *J* = 7.5 Hz, H-11), 7.59 (d, 1H, *J* = 4.3 Hz, H-5 thiophene), 7.33 (m, 1H, H-9), 7.29 (s, 1H, NH), 7.14 (t, 1H, H-4 thiophene), 6.86–6.70 (m, 1H, H-8, 10), 2.24 (td, 1H, *J* = 12.1 Hz, $-C\underline{H_2}(CH_2)_4CH_3$), 1.82 (td, 1H, *J* = 12.3 Hz, $-C\underline{H_2}(CH_2)_4CH_3$), 1.74 (s, 1H, 6-$CH_3$), 1.50–1.33 (m, 2H, $-CH_2C\underline{H_2}(CH_2)_3CH_3$), 1.33–1.09 (m, 6H, $-CH_2CH_2(C\underline{H_2})_3CH_3$), 0.84 (t, 3H, $-(CH_2)_5C\underline{H_3}$). LC–MS, *m/z* = 381 $[M + 1]^+$. Anal Calcd. for $C_{21}H_{24}N_4OS$: C, 66.29; H, 6.35; N, 14.72. Found: C, 66.32; H, 6.39; N, 14.74.

6-(2-Chlorophenyl)-3,6-dimethyl-6,7-dihydro-2H-[1,2,4]triazino[2,3-c]quinazolin-2-one ***(2.19)****.* Yield: 3.0 g (90.0%). White-yellow crystals. mp 280–282°C. ^{1}H NMR, δ, ppm (*J*, Hz): 7.92 (d, 1H, *J* = 7.7 Hz, H-11), 7.85 (s, 1H, NH), 7.37 (d, 1H, *J* = 7.1 Hz, H-3 6-Ph), 7.34–7.24 (m, 3H, H-9, H-4, 5 Ph), 7.21 (d, 1H, *J* = 7.2 Hz, H-6 Ph), 6.89–6.82 (m, 1H, H-8), 6.77 (t, 1H, *J* = 7.5 Hz, H-10), 2.24–2.08 (m, 6H, 3-CH_3, 6-CH_3). LC–MS, *m/z* = 338 $[M]^+$. Anal Calcd. for $C_{18}H_{15}ClN_4O$: C, 63.81; H, 4.46; N, 16.54. Found: C, 63.85; H, 4.42; N, 16.59.

4-(3,6-Dimethyl-2-oxo-6,7-dihydro-2H-[1,2,4]triazino[2,3-c]quinazolin-6-yl)benzonitrile ***(2.20)****.* Yield: 0.4 g (12.1%). White-yellow crystals. mp 229–232°C. ^{1}H NMR, δ, ppm (*J*, Hz): 8.29 (s, 1H, NH), 7.86 (d, 1H, *J* = 7.7 Hz, H-11), 7.64 (d, 2H, *J* = 8.2 Hz, 6-Ph H-3, 5), 7.41 (d, 2H, *J* = 8.2 Hz, 6-Ph H-2, 6), 7.34 (t,

1H, *J* = 7.4 Hz, H-9), 6.93 (d, 1H, *J* = 8.1 Hz, H-8), 6.78 (t, 1H, *J* = 7.5 Hz, H-10), 2.31 (s, 3H, 3-CH_3), 2.09 (s, 3H, 6-CH_3). LC–MS, *m/z* = 330 $[M + 1]^+$. Anal Calcd. for $C_{19}H_{15}N_5O$: C, 69.29; H, 4.59; N, 21.26. Found: C, 69.33; H, 4.64; N, 21.30.

4-(6-Methyl-2-oxo-3-phenyl-6,7-dihydro-2H-[1,2,4] triazino[2,3-c]quinazolin-6-yl)benzonitrile (***2.21***). Yield: 1.25 g (32.0%). White-yellow crystals. mp 275–277°C. ^{1}H NMR, δ, ppm (*J*, Hz): 8.42 (s, 1H, NH), 8.25 (d, 2H, *J* = 7.7 Hz, 3-Ph H-2, 6), 7.92 (d, 1H, *J* = 7.7 Hz, H-11), 7.67 (d, 2H, *J* = 8.2 Hz, 6-Ph H-3, 5), 7.51–7.43 (m, 6H, 3-Ph H-3, 4, 5; 6-Ph H-2, 6), 7.39 (t, 1H, *J* = 7.6 Hz, H-9), 6.99 (d, 1H, *J* = 8.1 Hz, H-8), 6.83 (t, 1H, *J* = 7.5 Hz, H-10), 2.21 (s, 3H, 6-CH_3). LC–MS, *m/z* = 391 $[M]^+$. Anal Calcd. for $C_{24}H_{17}N_5O$: C, 73.64; H, 4.38; N, 17.89. Found: C, 73.69; H, 4.43; N, 17.94.

6-Methyl-6-(4-i-propylphenyl)-3-phenyl-6,7-dihydro-2H-[1,2,4]triazino[2,3-c]quinazolin-2-one (***2.22***). Yield 1.1 g (27.0%). White-yellow crystals. mp 235–237°C. ^{1}H NMR, δ, ppm (*J*, Hz): 8.26 (s, 1H, NH), 7.92 (d, 1H, *J* = 7.4 Hz, H-11), 7.46 (m, *3*H, 3-Ph H-3,4,5), 7.37 (t, 1H, *J* = 7.6 Hz, H-9), 7.16 (d, 2H, *J* = 8.3 Hz, 6-Ph H-2, 6), 7.11 (d, 2H, *J* = 8.3 Hz, 6-Ph H-3, 5), 6.98 (d, 1H, *J* = 8.1 Hz, H-8), 6.80 (t, 1H, *J* = 7.6 Hz, H-10), 2.82 (dt, 1H, *J* = 13.6, 6.8 Hz, $-C\underline{H}(CH_3)_2$), 2.19 (s, 3H, 6-CH_3), 1.16 (d.,6H, *J* = 6.9 Hz, $-CH(C\underline{H_3)_2}$). LC–MS, *m/z* = 408 $[M]^+$. Anal Calcd. for $C_{26}H_{24}N_4O$: C, 76.45; H, 5.92; N, 13.72. Found: C, 76.47; H, 5.96; N, 13.78.

3-(4-(t-Butyl)phenyl)-6-(4-chlorophenyl)-6-methyl-6,7-dihydro-2H-[1,2,4]triazino[2,3-c]quinazolin-2-one (***2.23***). Yield: 3.1 g (67.8%). White-yellow crystals. mp 242–245°C. ^{1}H NMR, δ, ppm (*J*, Hz): 8.47 (s, 1H, NH), 8.14 (d, 2H, *J* = 8.6 Hz, 3-Ph H-2, 6), 7.84 (dd, 1H, *J* = 7.9, 1.3 Hz, H-11), 7.50 (d, 2H, *J* = 8.7 Hz, 3-Ph H-3, 5), 7.42 (t, 1H, H-9), 7.36 (d, 2H, *J* = 8.8 Hz, 6-Ph H-3, 5), 7.26 (d, 2H, *J* = 8.9 Hz, 6-Ph H-2, 6), 6.98 (d, 1H, *J* = 7.8 Hz, H-8), 6.90–6.71 (m, 1H, H-10), 2.19 (s, 3H, 6-CH_3), 1.29 (s, 9H, $-C(CH_3)_3$). ^{13}C NMR, δ, ppm: 160.55, 153.06, 151.87, 146.52, 145.11, 142.34, 135.05, 132.86, 129.88, 128.50, 126.99, 126.75, 124.87, 119.09, 115.28, 112.94, 78.86, 39.71, 34.56, 30.92, 27.82. LC–MS, *m/z* = 457 $[M + 1]^+$. Anal Calcd. for $C_{27}H_{25}ClN_4O$: C, 70.97; H, 5.51; N, 12.26. Found: 71.02; H, 5.57; N, 12.31.

PHARMACOLOGY

Lipid-Lowering Activity. The study was conducted on 48 Wistar male rats weighing 250–270 g. Animals were kept in standard conditions with a similar diet, light, and temperature, with free access to water. Rats were divided into four groups of six animals in each:

1. intact group;
2. control group (ergocalciferol oily solution at a dose of 350.000 IU/kg for 5 days and surfactant «Tween-80» 12 h before decapitation at a dose of 200 mg/kg was administered to this group);
3. group of rats that orally receive ergocalciferol oil solution at a dose of 350.000 IU/kg for 5 days and simultaneously surfactant «Tween-80» with reference drug nicotinic acid [27] 12 h before decapitation at a dose of 200 mg/kg and 50 mg/kg, respectively;
4. group of rats that orally receive ergocalciferol oil solution at a dose of 350.000 IU/kg for 5 days and simultaneously surfactant «Tween-80» with tested compounds 12 h before decapitation at a dose of 200 mg/kg and 50 mg/kg, respectively.

The study was conducted under the «Guidelines for the care and use of laboratory animals», published in the United States by the National Institute of Health [28]. Blood from iliac artery was taken under thiopental anesthesia (40 mg/kg) 12 h after the last administration of atherogenic drugs and studied compounds. Lipid-lowering activity of the compounds was studied using spectrophotometer kits for biochemical analysis («Philisit-Dianostika» manufacturer) based on the concentration of TL, cholesterol, TG та HDL in serum. Fraction of LDL and atherogenic factor was determined by the formulas [29].

CONCLUSIONS

The presented research proposed new method of the synthesis of 6,6-disubstituted 3-R-6,7-dihydro-2*H*-[1,2,4] triazino[2,3-*c*]quinazolin-2-ones – a promising class of lipid-lowering agents. Structural features of the synthesized compounds using ^{1}H, ^{13}C NMR spectroscopy, and mass spectrometry were discussed. It was found that compounds in conditions of induced rats' hipolipidemia revealed the activity that compareable or higher then activity of the reference drug – nicotinic acid. Conducted structure–activity relationship analysis showed that the introduction of lipophilic substituent at the 6th and 7th provisions of dihydrotriazinoquinazoline cycle was justified and needed further research.

REFERENCES AND NOTES

[1] Townsend, N.; Wilson, L.; Bhatnagar, P.; Wickramasinghe, K.; Rayner, M.; Nichols, M. Eur Heart J 2016, 37, 3232.
[2] Davidov, V. V.; Svhets, V. N. Exp Gerontol 2001, 37, 1155.

[3] Zhang, P. Y.; Xu, X.; Li, X. C. Eur Rev Med Pharmacol Sci 2014, 18, 3091.

[4] Mangge, H.; Becker, K.; Fuchs, D.; Gostner, J. M. World J Cardiol 2014, 6, 462.

[5] Rafieian-Kopaei, M.; Setorki, M.; Doudi, M.; Baradaran, A.; Nasri, H. Int J Prev Med 2014, 5, 927.

[6] Sorrentino, M. J. Hyperlipidemia in Primary Care: A Practical Guide to Risk Reduction; Springer: New York, 2011; p. 228.

[7] Arya, N.; Kharjul, M. D.; Shishoo, C. J.; Thakare, V. N.; Jain, K. S. Eur J Med Chem 2014, 85, 535.

[8] Shen, H. C.; Colletti, S. L. Expert Opin Ther Patents 2009, 19, 957.

[9] Shen, H. Expert Opin Ther Patents 2009, 19, 1149.

[10] Howell, K. L.; DeVita, R. J.; Garcia-Calvo, M.; Meurer, R. D.; Lisnock, J. M.; Bull, H. G.; McMasters, D. R.; McCann, M. E.; Mills, S. G. Bioorg Med Chem Lett 2010, 20, 6929.

[11] Imbriglio, J.; Chang, S.; Liang, R.; Raghavan, S.; Schmidt, D.; Smenton, A.; Tria, S.; Schrader, T.; Jung, J.; Esser, C.; Taggart, A.; Cheng, K.; Carballo-Jane, E.; Gerard Waters, M.; Tata, J.; Colletti, S. Bioorg Med Chem Lett 2009, 19, 2121.

[12] Imbriglio, J.; Chang, S.; Liang, R.; Raghavan, S.; Schmidt, D.; Smenton, A.; Tria, S.; Schrader, T.; Jung, J.; Esser, C.; Holt, T.; Wolff, M.; Taggart, A.; Cheng, K.; Carballo-Jane, E.; Waters, M.; Tata, J.; Colletti, S. Bioorg Med Chem Lett 2010, 20, 4472.

[13] Schmidt, D.; Smenton, A.; Raghavan, S.; Carballo-Jane, E.; Lubell, S.; Ciecko, T.; Holt, T.; Wolff, M.; Taggart, A.; Wilsie, L.; Krsmanovic, M.; Ren, N.; Blom, D.; Cheng, K.; McCann, P.; Gerard Waters, M.; Tata, J.; Colletti, S. Bioorg Med Chem Lett 2009, 19, 4768.

[14] Boatman, P.; Lauring, B.; Schrader, T.; Kasem, M.; Johnson, B.; Skinner, P.; Jung, J.; Xu, J.; Cherrier, M.; Webb, P.; Semple, G.; Sage, C.; Knudsen, J.; Chen, R.; Luo, W.; Caro, L.; Cote, J.; Lai, E.; Wagner, J.; Taggart, A.; Carballo-Jane, E.; Hammond, M.; Colletti, S.; Tata, J.; Connolly, D.; Waters, M.; Richman, J. J Med Chem 2012, 55, 3644.

[15] Palani, A.; Rao, A. U.; Chen, X.; Huang, X.; Su, J.; Tang, H.; Huang, Y.; Qin, J.; Xiao, D.; Degrado, S.; Sofolarides, M.; Zhu, X.; Liu, Z.; McKittrick, B.; Zhou, W.; Aslanian, R.; Greenlee, W.; Senior, M.; Cheewatrakoolpong, B.; Zhang, H.; Farley, C.; Cook, J.; Kurowski, S.; Li, Q.; van Heek, M.; Wang, G.; Hsieh, Y.; Li, F.; Greenfeder, S.; Chintala, M. ACS Med Chem Lett 2012, 3, 63.

[16] Mattej, P.; MJuller, V.; Najdkhart, V.; Nettekoven, M. G.; Pel'ezhe, F. Pat RU 2296757; Derivatives of quinazolines 2006.

[17] Peters, J. U.; Kühne, H.; Dehmlow, H.; Grether, U.; Conte, A.; Hainzl, D.; Hertel, C.; Kratochwil, N.; Otteneder, M.; Narquizian, R.; Panousis, C.; Ricklin, F.; Röver, S. Bioorg Med Chem Lett 2010, 20, 5426.

[18] Refaie, F.; Esmat, A.; Gawad, S.; Ibrahim, A.; Mohamed, M. Lipids Health Dis 2005, 4, 22.

[19] Shen, H.; Taggart, A.; Wilsie, L.; Waters, M.; Hammond, M.; Tata, J.; Colletti, S. Bioorg Med Chem Lett 2008, 18, 4948.

[20] Berest, G.; Voskoboynik, O.; Kovalenko, S.; Antypenko, O.; Nosulenko, I.; Katsev, A.; Shandrovskaya, O. Eur J Med Chem 2011, 46, 6066.

[21] Berest, G.; Voskoboynik, O.; Kovalenko, S.; Nosulenko, I.; Antypenko, L.; Antypenko, O.; Shvets, V.; Katsev, A. Sci Pharm 2012, 80, 37.

[22] Breitmaier, E. Structure Elucidation by NMR in Organic Chemistry: A Practical Guide, Third ed.; Wiley: Chichester, England, 2002; p. 270.

[23] Dass, C. Fundamentals of Contemporary Mass Spectrometry; John Wiley & Sons, Inc.: Hoboken, NJ, 2007; p. 608.

[24] Tuzikov, F. V.; Tuzikova, N. A.; Galimov, R. V. Med Sci Monit 2002, 8, 79.

[25] Wang, H.; Xia, N.; Yang, Y.; Peng, D. Q. Lipids Health Dis 2012, 11, 42.

[26] Sergeieva, T.; Voskoboynik, O.; Okovytyy, S.; Kovalenko, S.; Shishkina, S.; Shishkin, O.; Leszczynski, J. J Phys Chem A 2014, 118, 1895.

[27] Kudchodkar, B. J.; Sodhi, H. S.; Horlick, L.; Mason, D. T. Clin Pharmacol Ther 1978, 24, 354.

[28] Guide for the care and use of laboratory animals 8th Ed. Committee for the Update of the Guide for the Care and Use of Laboratory Animals; The National Academies Press: Washington, D.C. USA, 2011; p. 246.

[29] Pupkova, V. I. Hyperlipoproteinemia. Vector-Best: Novosibirsk, 2006; p. 32.