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Synthesis and structure of new 1,2,3-triazolyl substituted 1,3,5-triazines

Svetlana Mikhaylichenko*, Anthony Veloso, Kunjal Patel and Vladimir Zaplishny

Department of Physical and Environmental Sciences, University of Toronto Scarborough, Toronto, M1C 1A4, ON, Canada

**Corresponding author at: Department of Physical and Environmental Sciences, University of Toronto Scarborough, Toronto, M1C 1A4, ON, Canada. Tel.: +1.416.2877207; fax: +1.416.2877279. E-mail address: mikhay@utsc.utoronto.ca (S. Mikhaylichenko).*

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ABSTRACT

The reaction between monoazido derivatives of 1,3,5-triazine and CH-active carbonyl compounds were studied in order to obtain novel coupled heterocyclic systems with potential bioactivity. Reaction conditions were varied and optimized, a series 2,4-disubstituted derivatives of 6-(1*H*-1,2,3-triazol-1-yl)-1,3,5-triazines were obtained with good yield.

1. Introduction

It is well known that the 1,3,5-triazine and 1,2,3-triazole derivatives are compounds with high biological activities including antibacterial, antidote, as well as hypotensive, neuroleptic, cardio and carcinolytic activities. Some derivatives can be used as growth regulators, organic reactions catalysts, modifiers and polymer hardeners, etc. [1-5]. The most recent publication claims that some click-generated triazoles can inhibit serine hydrolase [6].

Earlier, we described a synthesis of new C-N connected 1,2,3-triazolyl-1,3,5-triazines (**TT**) from 2,4-disubstituted-6-azido-1,3,5-triazines by catalytic addition of substituted acetylenes to the azido group. These systems have two biologically active heterocycles in their structure and have a potential to possess a high biological activity. Similar C-N connected heterocyclic systems have been synthesized using triazine based monoazides or diazides and methylene active compounds such as acetylacetone and acetoacetic ester [7,8]. The active antidotes against phytotoxicity of 2,4-dichloro phenoxyacetic acid have been found among these derivatives [9,10].

It was interesting to notice, that using cyanoacetic acid esters as starting compounds in a similar reaction unexpectedly lead to the formation of a new connected heterocyclic system containing two six membered heterocycles-1,2,3,4-tetrazine and 1,3,5-triazine [11]. An even more exoticly connected heterocyclic aromatic system containing 1,3,5-triazine and 1,2,4-oxadiazol cycles has been synthesized by our group and reported recently [12].

2. Experimental

2.1. Instrumentation

The IR spectra were recorded on a BRUKER-Alpha P spectrophotometer. The ^{13}C and ^{1}H NMR spectra of all synthesized compounds were measured on a Varian-400 radiospectrometer in $CHCl_3$-d_1 and DMSO-d_6 solution accordingly. The mass spectra were obtained on a Finnigan MAT INCOS50 instrument (ionizing radiation energy was 70 eV). Elemental analysis was carried out on a Carlo-Erba model 1106 analyzer. The progress of the reactions was monitored and the purities of the compounds were checked by TLC on Polymer-2 with UV sensitive silufol layer plates in a acetone:hexane (1:1) system.

2.2. Synthesis

The initial 2,4-disubstituted-6-chloro-1,3,5-triazines, starting ammonium salts (**1**) and 2-azido-4,6-disubstituted-1,3,5-triazines (**2**) were prepared from cyanuric chloride according to procedures described earlier [13-15]. The solvents had been purified and dried according to procedures [16].

2.2.1. Synthesis of compounds 3a-r

Compounds **3a**-**3r** was synthesized according to following method (Scheme 1).

4,5-Dihydro-1-(4-methoxy-6-(pyperidin-1-yl)-1,3,5-triazin-2-yl)-5-methyl-N-phenyl-1H-1,2,3-triazole-4-carboxamide (**3b**): The 1.0 g (4.3 mmol) of 2-azido-4-methoxy-6-(piperid-1-yl)-1,3,5-triazine was dissolved in 10 mL anhydrous DMF and the mixture prepared from 1.52 g (8.6 mmol) of 3-oxo-*N*-phenylbutanamide and 0.89 g (8.8 mmol) of dry triethylamine in 10 mL DMF were added under the stirring conditions. The reaction mixture was stirred at room temperature for 48 hours. Progress of the reaction was monitored by IR-spectroscopy and TLC. After that, the reaction solution was poured out into 200 mL ice-cold water. The resulted solution was kept on ice bath for approximately 30 minutes to ensure maximum amount of white precipitate was obtained. The product was filtered and washed with cold water (3 x 30 mL) and dried at 50 °C.

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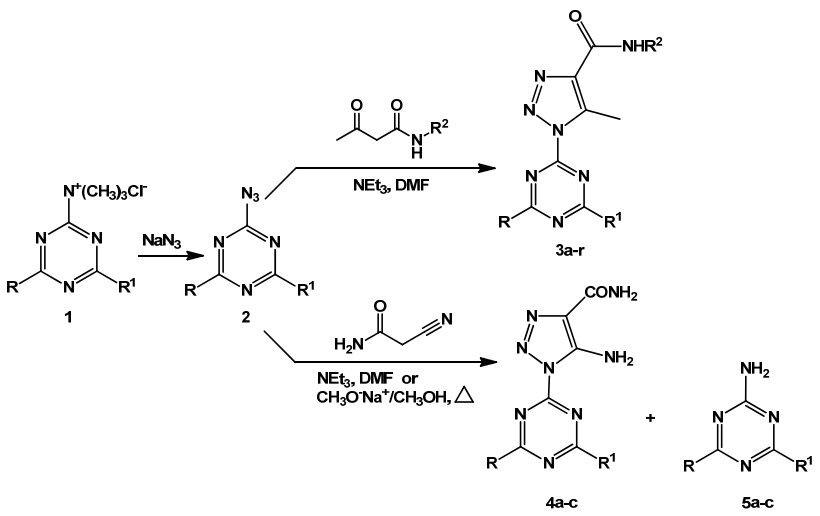


3a-c: R = OCH_3, R^1 = piperidino, R^2 = H **3a**, Ph **3b**, *o*-$CH_3OC_6H_4$ **3c**
3d-f: R = R^1 = piperidino, R^2 = H **3d**, Ph **3e**, *o*-$CH_3OC_6H_4$ **3f**
3g-i: R = R^1 = OCH_3, R^2 = H **3g**, Ph **3h**, *o*-$CH_3OC_6H_4$ **3i**
3j, **3k:** R = R^1 = OPh, R^2 = H **3j**, Ph **3k**
3l R = R^1 = NHEt, R^2 = Ph
3m-o: R = R^1 = morpholino, R^2 = H **3m**, Ph **3n**, *o*-$CH_3OC_6H_4$ **3o**
3p-r: R = OCH_3, R^1 = morpholino, R^2 = H **3p**, Ph **3q**, *o*-$CH_3OC_6H_4$ **3r**
4a, **5a:** R =OCH_3, R^1= morpholino
4b, **5b:** R = R^1 = piperidino
4c, **5c:** R = OCH_3, R^1 = piperidino

Scheme 1

After purification by crystallization from DMF:water (3:2) mixture, compound **3b** was obtained with the yield of 0.71 g (38.3%) (Table 1 and 2).

2.2.2. Synthesis of compounds 4a-c and 5a-c

Compounds **4a-c** and **5a-c** was synthesized according to following methods (Scheme 1). *5-amino-1-(4-methoxy-6-morpholino-1,3,5-triazin-2-yl)-1H-1,2,3-triazole-4-carboxamide* (**4a**):

Method 1: 0.35 g (1.48 mmol) of 2-azido-4-methoxy-6-morpholino-1,3,5-triazine and cyanoacetamide (0.107 g, 1.48 mmol) were dissolved in 10 mL of absolute methanol. A solution of Na (0.051 g, 2.2 mmol) in methanol (5 mL) was added in small portions at room temperature with stirring. The resulting solution was stirred for 30 min at room temperature and then refluxed for 2 hrs. Upon the completion of the reaction, it was cooled down and solvent evaporated under reduced pressure. The precipitate formed was washed with water and dried in air. The mixture of **4a** and **5a** was separated by column chromatography (acetone:hexane (1:1) mixture as eluent and 60 um silica). Compound **4a** was obtained with the yield of 0.18 g (25.5%) and compound **5a** was obtained with the yield of 0.11 g (23.7%) (Table 1 and 2).

Method 2: A mixture of 1.04 g (4.4 mmol) of cyanoacetamide and 0.44 g (4.4 mmol) of dry triethylamine in 10 mL DMF was added with stirring to the solution of 0.5 g (2.2 mmol) of 2-azido-4-methoxy-6-morholino-1,3,5-triazine in 10 mL anhydrous DMF. The reaction mixture was stirred at room temperature for 30 min and then heated with stirring at 60 °C for 3 hrs. Progress of the reaction was monitored by IR-spectroscopy and TLC. After that, the reaction solution was cooled down and poured into 200 mL of ice-cold water. The resulting solution was kept in an ice bath for approximately 30 minutes to ensure that a maximum amount of white precipitate was obtained. The product was filtered and washed with cold water (3 x 30 mL) and dried at 50 °C. After purification by crystallization from methanol, compound **4a** was obtained with the yield of 0.32 g (45.7%) (Table 1 and 2).

2.3. X-ray diffraction study

2.3.1. 4,5-Dihydro-1-(4-methoxy-6-morpholino-1,3,5-triazin-2-yl)-N-(2-methoxyphenyl)-5-methyl-1H-1,2,3-triazole-4-carboxamide (3r)

Crystals were grown from a iso-propanol:water (3:2) system solution. The prismatic crystals belong to the triclinic system; the unit cell parameters: a = 9.2374(5) Å, b = 10.4329(8) Å, c = 11.8262(6) Å, α = 79.506(3)°, β = 73.461(3)°, γ = 88.958(3)°. Z = 2, d = 1.431 Mg/ m^3, V = 1073.61(11) Å^3 space group P-1 (Figure 1 and 2). X-ray diffraction data were collected on an automated Bruker-Nonius Kappa-CCD diffractometer. β-Filtered Mo-$K\alpha$ radiation were measured using a combination of ϕ scans and ω scans with κ offsets, to fill the Ewald sphere. A total of 11018 reflections were measured. Of which 4855 reflections were with I>2δ(I). The structure was solved and refined using SHELXTL v6.1 [17,18] for full-matrix least-squares refinement that was based on F^2. All H atoms were included in calculated positions and allowed to refine in riding-motion approximation with U_{iso} tied to the carrier atom. The data was processed using the Denzo-SMN package [19]. Absorption corrections were carried out using SORTAV [20].

2.3.2. 4-Methoxy-6-(piperidin-1-yl)-1,3,5-triazin-2-amine (5a)

Crystals were grown from an iso-propanol:water (3:2) system solution. The prismatic crystals belong to the triclinic system; the unit cell parameters: a = 8.3170(3) Å, b = 10.4123(4) Å, c = 13.3186(5) Å, α = 107.141(2)°, β = 99.074(2)°, γ = 91.9490(19)°. Z = 4, d = 1.282 Mg/ m^3, V = 1084.39 (11) Å^3 space group P-1 (Figure 3 and 4).

Table 1. IR, ^{1}H- and ^{13}C- NMR and Mass spectra of 1,3,5-triazinyl-triazoles derivatives.

Compound	IR-spectrum, γ , *cm*$^{-1}$	^{1}H NMR, δ, *ppm*	Molecular ion, *m/z*, *(I, %)*
3a	3388.18 (m, NH); 2927.74, 2857.80 (w, CH Alk); 1669.26 (st., C=O); 1591.30, 1555.19, 1498.44 (st., + m., C=C- + C=N conj.); 1255.59 (m., -C-N); 1196.13, 1137.17, 1088.66, 1007.09 (m., C-O-C)	8.03 (2H, s, NH_2CO); 4.06 (3H, s, OCH_3); 3.84 (4H, t, N-CH_2, *J*= 5.0 Hz); 2.28 (3H, s, C-CH_3); 2.6 (3H, s, CH_3); 1.59-1.67 (6H, m, Σ $3CH_2$ in piperidyl)	318 (54)
3b	3379.29 (m, NH); 2923.19, 2852.61 (w., CH Ph); 1677.78 (st., C=O); 1598.02, 1570.00, 1497.41 (st. + m., C=C- + C=N conj.); 1239.09 (m., -C-N); 1191.37, 1113.81, 1078.17, 1027.30 (m., C-O-C)	8.83 (1H, s, NH-Ph); 7.71, 7.52, 7.27 (5H, m, CH in C_6H_5); 4.12 (3H, s, O-CH_3); 2.98 (3H, s, CCH_3); 1.53-1.63 (6H, m, Σ CH_2 in piperidyl)	394 (71)
3c	3392.14 (m., NH); 2929.37, 2860.64 (w., CH Ph + Alk); 1663.12 (st., C=O); 1605.02, 1543.28, 1497.93 (st., + m., -C=C + -C=N conj.); 1255.35 (m., -C-N); 1188.27, 1162.13, 1090.25, 1022.92 (m., C-O-C); 749.19 (w. C*sp*^{2}–H o.o.p. bending, 1.2-C_6H_4)	8.48 (1H, s, NH-Ph); 7.28, 7.06, 6.93 (4H, m, CH in C_6H_4); 4.06 (6H, s, O-CH_3); 3.83 (4H, t, NCH_2, *J*=8 Hz; 3.03 (3H, s, C-CH_3); 1.68 (6H, m, Σ $3CH_2$ in piperidyl)	424 (83)
3d	3380.74 (m., NH); 2928.87, 2857.73 (w., CH Alk); 1659.46 (st., C=O); 1600.18, 1538.44, 1501.02 (st. + m., -C=C + -C=N conj.); 1254.66 (m., -C-N); 1149.93, 1103.89, 1088.94 1012.88 (m., C-O-C)	9.03 (2H, s, NH_2CO); 3.82, (8H, t, Σ CH_2N) *J*=7.6 Hz); 2.87 (3H, s, CCH_3); 1.64 (12H m, Σ6 CH_2 in piperidyl)	371 (90)
3e	3366.73 (m., NH); 2929.21, 2856.28 (w., CH Ph + Alk); 1657.03 (st., C=O); 1584.44, 1534.77, 1493.27 (st. + m., C=C- + C=N-conj.); 1255.47 (-C-N); 1199.03, 1128.28, 1090.00, 1033.19 (C-O-C)	9.13 (1H, s, NHPh); 7.72, 7.35, 7.12 (5H, m, CH in C_6H_5); 3.80, (8H, t, Σ CH_2N, *J*=4.0 Hz); 2.92 (3H, s, CCH_3); 1.59 (12H m, Σ6 CH_2 in piperidyl)	447 (55)
3f	3394.11 (m., NH); 2909.98, 2861.27 (w., CH Ph + Alk); 1664.98 (st., C=O); 1571.51, 1530.30, 1498.00 (st. + m., C=C- + C=N-conj.); 1255.24 (-C-N); 1183.27, 1113.13, 1090.39, 1021.22 (C-O-C); 748.13 (w. C*sp*^{2}–H o.o.p. bending, 1.2-C_6H_4)	9.28 (1H, s, NH-Ph); 7.32, 7.04, 6.91 (4H, m, CH in C_6H_4); 3.98 (3H, s, O-CH_3); 3.80 (8H, t, NCH_2, *J*=6.3 Hz); 2.43 (3H, s, C-CH_3); 1.67 (12H, m, Σ6 CH_2 in piperidyl)	477 (80)
3g	3312.76 (m., NH); 1678.59 (st., C=O); 1604.29, 1513.40, 1497.18 (st. + m., C=C- + C=N-conj.); 1183.47, 1123.73, 1059.08, 1008.32 (C-O-C)	7.68 (2H, s, $CONH_2$); 3.93 (6H, s, OCH_3); 2.51 (3H, s, C-CH_3)	265 (93)
3h	3381.67 (m., NH); 2983.13, (w., CH Ph); 1687.24 (st., C=O); 1603.79, 1524.93, 1501.81 (st. + m., C=C- + C=N-conj.); 1191.32, 1107.33, 1081.11, 1011.19 (C-O-C)	9.15 (1H, s, NHPh); 7.75 (2H, d, CH in C_6H_5, *J*=6.8 Hz); 7.43, 7.19 (3H, m, CH in C_6H_5); 2.83 (3H, s, OCH_3); 2.06 (3H, s, CCH_3)	341 (66)
3i	3312.76 (m., NH); 3074.07, 2932.79 (w., CH Ph + Alk); 1678.59 (st., C=O); 1606.29, 1513.40, 1495.87 (st. + m., C=C- + C=N-conj.); 1183.47, 1123.73, 1085.08, 1008.32 (C-O-C); 717.31 (w. C*sp*^{2}–H o.o.p. bending, 1.2-C_6H_4)	8.28 (1H, s, NHPh); 7.50 (2H, d, CH in C_6H_4, *J*=7.9 Hz); 7.10, 6.95 (2H, m, CH in C_6H_4); 3.95 (9H, s, OCH_3); 2.17 (3H, s, CCH_3)	371 (55)
3j	3305.19 (m., NH); 3059.43 (w., CHPh); 1680.13 (st., C=O); 1596.77, 1564.76, 1497.00 (m., C=C- + C=N-conj.); 1204.14, 1119.21, 1084.92, 1023.51 (C-O-C)	8.11 (2H, s, $CONH_2$); 7.45 (4H, d, CH in C_6H_5, *J*=8.0 Hz); 7.21, 7.05 (6H, m, CH in C_6H_5); 2.18 (3H, s,CCH_3)	389 (81)
3k	3375.98 (m., NH); 2934.53, (w., CH Ph); 1682.25 (st., C=O); 1600.38, 1516.38, 1496.56 (st. + m., C=C- + C=N-conj.); 1190.05, 1169.13, 1061.68, 1013.09 (C-O-C)	8.36 (1H, s, PhNH); 7.36 (6H, d., CH in C_6H_5, *J*=6.6 Hz); 7.21, 7.05 (9H, m, CH in C_6H_5); 2.11 (3H, s,CCH_3)	465 (43)
3l	3381.08 (m., NH); 3034.87, 2969.68 (w., CH Ph + Alk); 1679.71 (st., C=O); 1599.45, 1556.31, 1503.48 (st. + m., C=C- + C=N-conj.); 1313.27 (-C-N)	9.18 (1H, s, NHPh); 7.78 (2H, d, CH in C_6H_5, *J*=7.2 Hz); 7.40, 7.15 (3H, m, CH in C_6H_5); 3.94 (1H, s, CH_2NH); 3.80 (4H, q, CH_2CH_3, *J*=7.6 Hz); 2.76 (3H, s, C-CH_3); 1.35 (3H, t, CH_2CH_3, *J*=7.6 Hz)	367 (70)
3m	3358.27, 3289.60 (m., NH_2CO); 1678.24 (st., C=O); 1596.35, 1568.18, 1499.36 (st. + m., C=C- + C=N-, conj.); 1241.08 (m., -C-N); 1196.32, 1107.68, 1069.58, 1004.08 (st. + m., C-O-C)	8.17 (2H, s, $CONH_2$); 3.94 (8H, m, Σ$4CH_2O$); 3.72 (8H, m, Σ $4CH_2N$); 2.19 (3H, s, CCH_3)	375 (80)
3n	3375.51 (m., NH); 2977.25, 2899.16 (w., CH Ph + Alk); 1686.32 (st., C=O); 1599.14, 1553.19, 1501.03 (st. + m., C=C- + C=N-, conj.); 1241.51 (m., C-N); 1188.47, 1108.18, 1058.13, 1001.96 (st. + m., C-O-C)	9.02 (1H, s, PhNH); 7.54 (2H, d, CH in C_6H_5, *J*=7.3 Hz); 7.36, 7.14 (8H, m, CH in C_6H_5); 3.90 (8H, m, Σ4 CH_2O); 3.75 (8H, m, Σ 4 CH_2N); 2.21 (3H, s, CCH_3)	451 (44)
3o	3323.33 (m., NH); 2981.17, 2893.23 (w., CH Ph + Alk); 1681.83 (st., C=O); 1603.11, 1541.18, 1506.87 (m, -C=C + -C=N, conj.); 1250.18 (m, C-N); 1177.09, 1107.08, 1063.24, 1001.22 (st. + m., C-O-C); 735.01 (m. C*sp*^{2}–H o.o.p. bending, 1.2-C_6H_4)	9.09 (1H, s, PhNH); 7.65, 7.34, 7.16 (4H, m, CH in C_6H_4); 3.94 (3H, s, OCH_3); 3.88 (8H, m, $4CH_2O$); 3.70 (8H, m, Σ 4 CH_2N); 2.13 (3H, s, CCH_3)	481 (39)
3p	3886.01, 3296.37 (m., NH_2CO); 1669.96 (st., C=O); 1600.33, 1570.03, 1503.52 (st. + m., C=C- + C=N-, conj.); 1244.27 (m., C-N); 1191.47, 1108.61, 1062.60, 1007.13 (st. + m., C-O-C)	8.53 (2H, s, $CONH_2$); 3.98 (3H, s, OCH_3); 3.83 (4H, m, Σ$2CH_2O$); 3.76 (4H, m, Σ $2CH_2N$); 1.93 (3H, s, CCH_3)	320 (40)
3q	3344.13 (m., NH); 2962.74, 2862.16 (w., CH Ph + Alk); 1680.12 (st., C=O); 1597.02, 1541.27, 1499.28 (st. + m., C=C- + C=N-, conj.); 1251.97 (m., C-N); 1180.67, 1111.08, 1058.13, 1002.27 (st. + m., C-O-C)	9.09 (1H, s, PhNH); 7.71 (2H, d, CH in C_6H_5, *J*=7.4 Hz); 7.26, 7.12 (3H, m, CH in C_6H_5); 4.08 (3H, s, OCH_3); 3.93 (4H, m, Σ $2CH_2O$); 3.73 (4H, m, Σ 2 CH_2N); 1.88 (3H, s, CCH_3)	396 (37)
3r	3350.33 (m., NH); 2982.07, 2825.90 (w., CH Ph + Alk); 1682.33 (st., C=O); 1598.69, 1547.27, 1508.76 (st. + m., C=C- + C=N-, conj.); 1266.11 (m., C-N); 1193.75, 1105.74, 1067.22, 1000.16 (st. + m., C-O-C); 746.37 (w. C*sp*^{2}–H o.o.p. bending, 1.2-C_6H_4)	9.11 (1H, s, PhNH); 7.74, 7.38, 7.20 (4H, m, CH in C_6H_4); 4.06 (3H, s, OCH_3); 3.95 (4H, m, Σ $2CH_2O$); 3.79 (4H, m, Σ 2 CH_2N); 1.93 (3H, s, CCH_3)	426 (55)

Table 1. IR, ^{1}H- and ^{13}C- NMR and Mass spectra of 1,3,5-triazinyl-triazoles derivatives.

Compound	IR-spectrum, γ , cm^{-1}	^{1}H NMR, δ, *ppm*	Molecular ion, *m/z, (I_i, %)*
4a	3383.70, 3331.65 (m., NH_2); 3174.98 (m., NH); 2875.76 (w., =CH) 1660.98 (st., C=O); 1575.90, 1524.33, 1464.67 (st. + m., C=C- + C=N-, conj.); 1283.19, 1197.50, 1111.55, 1070.44 (st. + m., C-O-C and C-N)	13.65 (1H, s, br. NH_2); 7.12 (1H, s, br. NH_2); 5.18 (2H, .s, br., $CONH_2$); 3.97 (3H, s, OCH_3); 3.85 (4H, m, Σ $2CH_2O$); 3.75 (4H, m, Σ 2 CH_2N)	321 (35)
4b	3367.02, 3349.49 (m., NH_2); 3191.90 (m., N-H); 2927.04, 2852.98 (w., =CH); (w., C=NH); 1665.06 (m., C=O); 1633.61, 1573.68, 1499.41 (st. + m., C=C- + C=N-, conj.); 1242.80, 1150.48 (m., C-N)	13.51 (1H, s, br. NH_2); 6.81 (1H, s, br., NH_2); 5.48 (2H, s, br., $CONH_2$); 3.64 (8H, m, Σ N-CH_2); 1.52 (12H, Σ C-CH_2)	373 (100)
4c	3465.23, 3317.75 (m., NH_2); 3180.54 (m., N-H); 2938.64, 2862.85 (w., =CH); 1679.89 (st., C=O); 1595.87, 1513.38, 1476.49 (st. + m., C=C- + C=N-, conj.); 1255.44, 1206.12, 1125.79, 1025.16 (st. + m., C-O-C and C-N)	13.72 (1H, s, br., NH_2); 7.18 (1H, s, br., NH_2); 5.52 (2H, s, br, $CONH_2$) 3.98 (3H, s, OCH_3); 3.78 (4H, m, N-CH_2); 1.62 (6H, m, C-CH_2)	319 (65)
5a	3371.37 (m., NH_2); 1575.90, 1524.33, 1464.67 (st. + m., C=C- + C=N-, conj.); 1249.64, 1206.12, 1124.69, 1109.46, 1005.24 (st. + m., C-O-C and C-N)	4.96 (2H.s, br., NH_2); 3.97 (3H, s, OCH_3); 3.85 (4H, m, Σ $2CH_2O$); 3.75 (4H, m, Σ 2 CH_2N)	211 (100)
5b	3372.51 (m., NH_2); 1575.10, 1520.37, 1483.03 (st. + m., C=C- + C=N-, conj.); 1633.61, 1573.68, 1499.41 (st. + m., C=C- + C=N-, conj.); 1242.99, 1170.12 (m., C-N)	4.65 (2H, s, br., NH_2); 3.65 (10H, m, Σ C-CH_2, N-CH_2)	272 (100)
5c	3369.42 (m., NH_2); 1585.10, 1512.37, 1473.03 (st. + m., C=C- + C=N-, conj.); 1264.82, 1208.45, 1118.49, 1070.44 (st. + m., C-O-C and C-N)	4.92 (2H, s, br., NH_2); 3.88 (3H, s, OCH_3); 3.73 (4H, m, Σ 2 CH_2N); 1.75 (6H, m, CH_2)	209 (100)

Table 2. Characteristics of Synthesized compounds **3a-r**, **4a-c**, and **5a-c**.

Compound	Empirical formula	Found, % / Calculated, %			Melting point, °C	Yield, %
		C	H	N		
3a	$C_{13}H_{18}N_8O_2$	48.83 49.05	8.32 8.49	35.09 35.20	244-246	30.8
3b	$C_{19}H_{22}N_8O_2$	57.67 57.86	5.81 5.62	28.56 28.41	184-186	35.3
3c	$C_{20}H_{24}N_8O_3$	55.90 56.12	5.52 5.70	23.50 23.40	133-135	36.5
3d	$C_{17}H_{25}N_9O$	55.16 54.97	6.59 6.78	34.07 33.94	205-208	29.7
3e	$C_{23}H_{29}N_9O$	61.58 61.73	6.41 6.53	28.03 28.17	222-224	66.1
3f	$C_{24}H_{31}N_9O_2$	60.53 60.36	6.47 6.54	26.67 26.40	210-212	39.4
3g	$C_9H_{11}N_7O_3$	40.89 40.76	3.99 4.18	37.09 36.97	243-245	34.1
3h	$C_{15}H_{15}N_7O_3$	52.62 52.78	4.51 4.43	28.82 28.73	265-267	77.0
3i	$C_{16}H_{17}N_7O_4$	51.59 51.75	4.78 4.61	26.49 26.40	242-243	58.6
3j	$C_{19}H_{15}N_7O_3$	58.46 58.61	3.99 3.88	25.09 25.18	244-246	41.7
3k	$C_{25}H_{19}N_7O_3$	64.71 64.51	3.91 4.11	20.93 21.06	187-189	43.3
3l	$C_{17}H_{21}N_9O$	55.36 55.57	5.79 5.76	34.45 34.31	167-169	83.0
3m	$C_{15}H_{21}N_9O_3$	48.18 47.99	5.82 5.64	33.43 33.58	318-320	82.5
3n	$C_{21}H_{25}N_9O_3$	55.67 55.87	5.71 5.58	27.76 27.92	230-231	85.9
3o	$C_{22}H_{27}N_9O_4$	55.00 54.88	5.52 5.65	26.04 26.18	254-255	61.0
3p	$C_{12}H_{16}N_8O_3$	45.16 44.99	4.86 5.04	34.77 34.98	217-218	84.1
3q	$C_{18}H_{20}N_8O_3$	54.68 54.54	4.89 5.09	28.40 28.27	159-161	90.3
3r	$C_{19}H_{22}N_8O_4$	53.33 53.52	5.37 5.20	26.17 26.28	207-209	75.8
4a	$C_{11}H_{15}N_9O_3$	35.89 36.09	3.62 3.79	41.92 42.09	187-188	25.5 (Method 1) 45.7 (Method 2)
4b	$C_{15}H_{22}N_{10}O$	55.32 55.53	3.21 3.37	28.82 28.78	250-252	20.1 (Method 1) 53.5 (Method 2)
4c	$C_{12}H_{17}N_9O_2$	45.30 45.14	5.11 5.37	39.37 39.48	251-253	24.7 (Method 1) 65.3 (Method 2)
5a	$C_8H_{13}N_5O_2$	45.62 45.49	6.03 6.20	33.01 33.16	132-134	23.7
5b	$C_{13}H_{22}N_6$	59.67 59.50	8.59 8.45	32.13 32.03	145-147	19.2
5c	$C_9H_{15}N_5O$	51.83 51.66	5.09 5.23	33.39 33.47	128-130	22.4

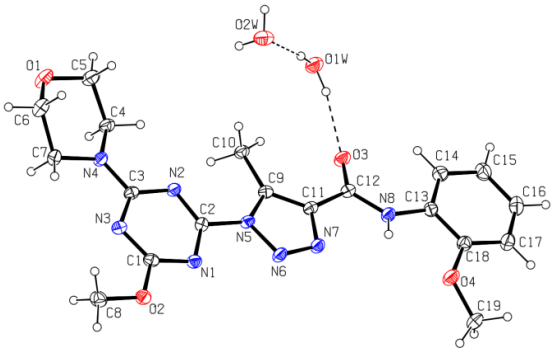


Figure 1. Crystal structure of compound **3r**.

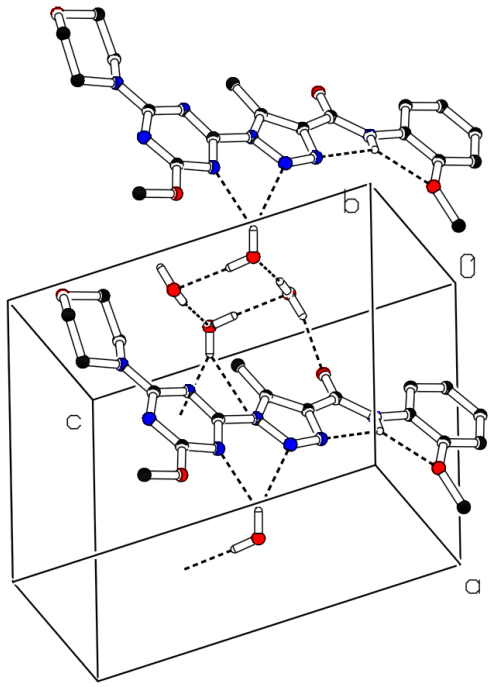


Figure 2. Crystal packing diagram of compound **3r**.

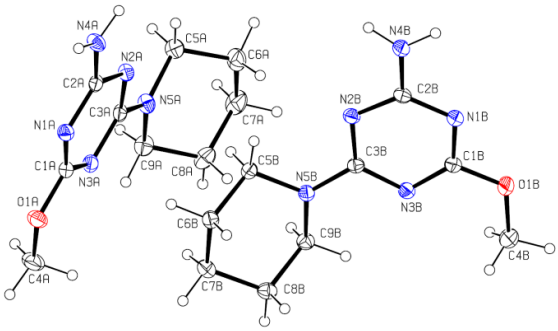


Figure 3. Crystal structure of compound **5a**.

X-ray diffraction data were collected on an automated Bruker-Nonius Kappa-CCD diffractometer. β-Filtered Mo-*Kα* radiation were measured using a combination of ϕ scans and ω scans with κ offsets, to fill the Ewald sphere. A total of 12902 reflections were measured. Of which 4909 reflections were with $I>2\delta(I)$. The structure was solved and refined using SHELXTL V6.1 [17,18] for full-matrix least-squares refinement that was based on F^2. All H atoms were included in calculated positions and allowed to refine in riding-motion approximation with U_{iso} tied to the carrier atom. The data was processed using the Denzo-SMN package [19]. Absorption corrections were carried out using SORTAV [20].

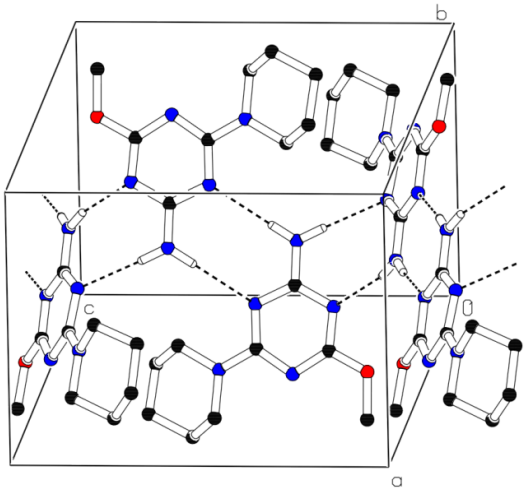


Figure 4. Crystal packing diagram of compound **5a**.

2.3.3. 1-(4-Methoxy-6-morpholino-1,3,5-triazin-2-yl)-5-methyl-1H-1,2,3-triazole-4-carboxamide (3a)

Crystals were grown from a iso-propanol:water (3:2) system solution. The prismatic crystals belong to the triclinic system; the unit cell parameters: a = 8.3159(3) Å, b = 9.6944(3) Å, c = 10.0824(4) Å, α = 78.237(3)°, β = 85.529(3)°, γ = 84.457(1)°. Z = 2, d = 1.413 Mg/ m³, V = 790.61(5) Å³ space group P-1 (Figure 5 and 6). X-ray diffraction data were collected on an automated Bruker-Nonius Kappa-CCD diffractometer. β-Filtered Mo-Kα radiation were measured using a combination of ϕ scans and ω scans with κ offsets, to fill the Ewald sphere. A total of 6348 reflections were measured. Of which 3095 reflections were with I>2δ(I). The structure was solved and refined using SHELXTL V6.1 [17,18] for full-matrix least-squares refinement that was based on F^2. All H atoms were included in calculated positions and allowed to refine in riding-motion approximation with U_{iso} tied to the carrier atom. The data was processed using the Denzo-SMN package [19]. Absorption corrections were carried out using SORTAV [20].

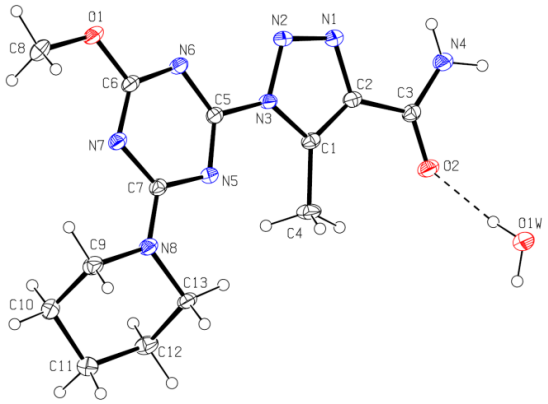
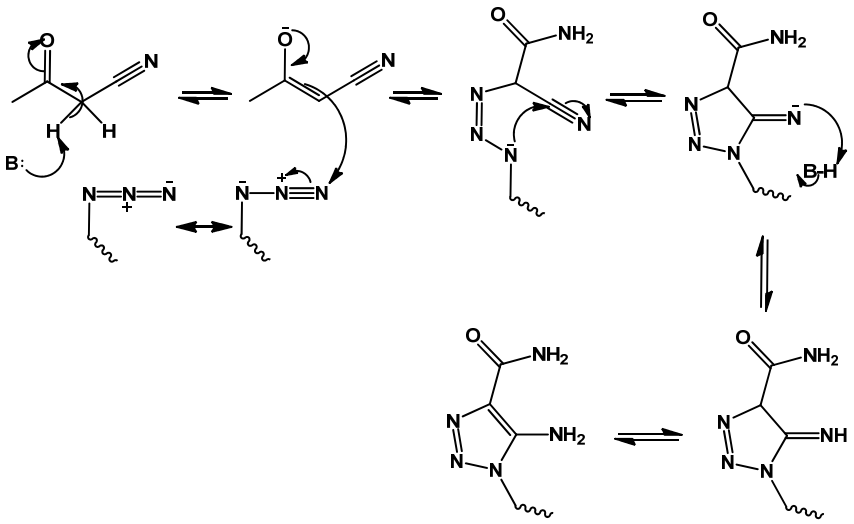


Figure 5. Crystal structure of compound **3a**.



Scheme 2

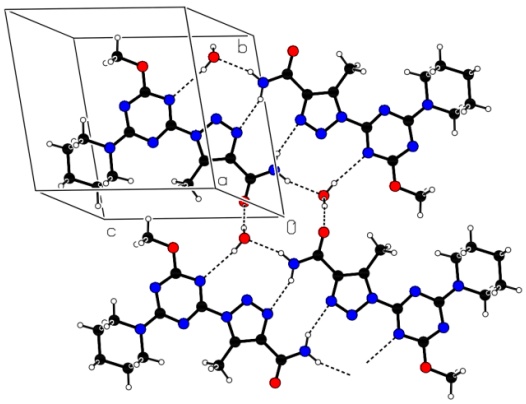


Figure 6. Crystal packing diagram of compound **3a**.

3. Results and discussion

As it follows from the introductory part, to synthesize new potentially bioactive **TT** using other methylene active compounds, and also to expand the row of existing **TTs** using different derivatives of 1,3,5-triazines was an interesting task. We chose a three step synthesis according to the Scheme 1.

Known, very active and stable quaternary salts (**1**) were used as starting compounds for these syntheses [13]. These salts react very smoothly with equimolar amounts of sodium azide under the room temperature conditions in water as it has been described previously [10]. Final products of this reaction were monoazides (**2**). Products **2** were subject to react with CH-active aromatic dicarbonyl compounds. The most effective catalyst for this addition-cyclization reaction was found to be triethylamine in anhydrous DMF. Heating was not necessary and yields for the formation of the compounds **3a-r** were relatively high (30-90%) and overall reaction time was around 48-60 hrs. We found that increasing the reaction temperature leads to the decomposition of desired compounds and formation of multiple side products.

Previously, we reported that using esters of cyanoacetic acid as a methylene active reagent in reaction with 2-azide-4,6-disubstituted-1,3,5-triazines lead to the formation of six-membered 1,2,3-triazinyl-1,2,3,4-tetrazines [11]. It was interesting to compare different reaction conditions for the similar reaction of azido-derivatives of 1,3,5-triazine with less reactive cyanoacetamide (CAA) as a reagent. The reaction between azido-1,3,5-triazine derivatives and cyanoacetamide using sodium methylate as a catalyst unexpectedly produced two products, the amino derivatives of triazolo-1,3,5-triazines **4**, and the amino derivative of 1,3,5-triazine **5**. We think that possible explanation for the formation of the unexpected 2-amino-4,6-disubstituted-1,3,5-triazines could be the decomposition of azides to unstable nitrenes [7,23] with following protonation under harsh reaction conditions. On the other hand, the reaction between azido-derivatives of 1,3,5-triazine and cyanoacetamide with triethylamine as a catalyst and dry DMF as a solvent, smoothly leads to the formation of connected 1,2,3-triazolyl-1,3,5-triazines heterocyclic system **4** with good yields. Both reaction conditions require elevated temperatures. The formation of compounds **4** could be explained using the given reaction mechanism in Scheme 2.

The reaction produced unstable imine derivative of 1,2,3-triazole which rearranged spontaneously to the more stable aromatic 1,2,3-triazole cycle.

The reaction rates were monitored by IR-spectroscopy and TLC. All synthesized derivatives **3a-r**, **4a-c**, and **5a-c** are white crystals with the wide variety of melting points (Table 2). All were soluble in aprotic solvents like DMF, dioxane, or DMSO, slightly soluble in acetone, and insoluble in water or hydrocarbons.

The structures of all synthesized compounds were proven by IR, ^{1}H NMR, and mass spectroscopy data (Table 1). The fine structures of compounds **3a**, **3r** and **5a** were studied by X-ray diffraction method (Figure 1-6 and Table 3-11).

IR-spectroscopy data of the compounds **3-5** have variable intensity, sometimes broad absorption bands as well as stretching vibrations typical for the functional groups in their structure. IR-spectroscopy data for the valence stretching of the NH-group in compounds **3a-r** showed one medium absorption band in the area 3394-3305 cm^{-1} and strong -C=O signal for the amide group in the area of 1663-1687 cm^{-1}. Compounds **4a-c** have two medium intensity absorption bands for the amide group in the area 3383-3317 cm^{-1} and one signal in the area of 3174-3191 cm^{-1} for the amine group. The valence bending for the carbonyl group -C=O of the compounds **4a-c** was observed in the area of 1660-1679 cm^{-1}, respectively.

Table 3. Selected interatomic distances in molecule **3r**.

Bond	d (Å)	Bond	d (Å)
O(3)-C(12)	1.232(3)	N(8)-C(13)	1.409(3)
O(4)-C(18)	1.380(3)	C(9)-C(11)	1.378(3)
O(4)-C(19)	1.432(3)	C(9)-C(10)	1.484(3)
N(5)-C(9)	1.368(3)	C(11)-C(12)	1.474(3)
N(5)-N(6)	1.381(2)	C(13)-C(14)	1.383(3)
N(5)-C(2)	1.433(3)	C(13)-C(18)	1.395(3)
N(6)-N(7)	1.296(3)	C(14)-C(15)	1.388(3)
N(7)-C(11)	1.371(3)	C(15)-C(16)	1.388(3)
N(8)-C(12)	1.351(3)	C(16)-C(17)	1.385(4)

Table 4. Bond angles in molecule **3r**.

Angle	φ (°)	Angle	φ (°)
C(5)-O(1)-C(6)	109.68(17)	N(3)-C(3)-N(2)	124.39(18)
C(1)-O(2)-C(8)	117.00(17)	N(4)-C(4)-C(5)	110.9(2)
C(18)-O(4)-C(19)	118.03(18)	O(1)-C(5)-C(4)	111.6(2)
C(2)-N(1)-C(1)	111.14(17)	O(1)-C(6)-C(7)	111.4(2)
C(2)-N(2)-C(3)	112.93(18)	N(4)-C(7)-C(6)	110.37(19)
C(1)-N(3)-C(3)	113.83(19)	N(5)-C(9)-C(11)	103.19(18)
C(3)-N(4)-C(7)	122.83(19)	N(5)-C(9)-C(10)	126.97(18)
C(7)-N(4)-C(4)	114.28(17)	C(11)-C(9)-C(10)	129.8(2)
C(9)-N(5)-N(6)	111.21(16)	N(7)-C(11)-C(9)	109.3(2)
C(9)-N(5)-C(2)	130.88(17)	N(7)-C(11)-C(12)	120.98(18)
N(6)-N(5)-C(2)	117.89(17)	C(9)-C(11)-C(12)	129.7(2)
N(7)-N(6)-N(5)	106.42(17)	O(3)-C(12)-N(8)	124.1(2)
N(6)-N(7)-C(11)	109.87(17)	O(3)-C(12)-C(11)	122.88(19)
C(12)-N(8)-C(13)	129.3(2)	N(8)-C(12)-C(11)	113.0(2)
N(3)-C(1)-O(2)	120.1(2)	C(14)-C(13)-C(18)	119.7(2)
N(3)-C(1)-N(1)	127.8(2)	C(14)-C(13)-N(8)	124.55(19)
O(2)-C(1)-N(1)	112.07(18)	C(18)-C(13)-N(8)	115.7(2)
N(2)-C(2)-N(1)	129.78(19)	C(13)-C(14)-C(15)	120.1(2)
N(2)-C(2)-N(5)	115.36(18)	C(16)-C(15)-C(14)	119.6(2)
N(1)-C(2)-N(5)	114.86(17)	C(17)-C(16)-C(15)	121.3(2)
N(4)-C(3)-N(3)	118.42(19)	C(16)-C(17)-C(18)	118.6(2)
N(4)-C(3)-N(2)	117.18(19)	O(4)-C(18)-C(17)	124.56(19)
O(4)-C(18)-C(13)	114.74(19)	C(17)-C(18)-C(13)	120.7(2)

Table 5. Hydrogen bonds for compound **3r** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(8)-H(1N)...N(7)	0.85(3)	2.26(3)	2.709(3)	113(2)
O(1W)-H(1WA)...O(2W)	0.85	2.02	2.866(2)	174.7
O(1W)-H(1WB)...O(3)	0.85	1.99	2.829(2)	168.6
O(2W)-H(2WA)...N(1)#1	0.85	2.35	3.096(2)	146.5
O(2W)-H(2WA)...N(6)#1	0.85	2.44	3.170(3)	144.1

Symmetry transformations used to generate equivalent atoms: #1 *x*-1, *y*, *z*

Table 6. Selected interatomic distances in molecule **5a**.

Bond	d (Å)	Bond	d (Å)
O(1A)-C(1A)	1.3431(18)	N(4A)-H(1N)	0.876(19)
O(1A)-C(4A)	1.441(2)	N(4A)-H(2N)	0.911(19)
N(1A)-C(1A)	1.330(2)	N(5A)-C(3A)	1.352(2)
N(1A)-C(2A)	1.352(2)	N(5A)-C(9A)	1.460(2)
N(2A)-C(3A)	1.3428(19)	N(5A)-C(5A)	1.462(2)
N(2A)-C(2A)	1.3526(19)	C(5A)-C(6A)	1.527(2)
N(3A)-C(1A)	1.3211(19)	C(6A)-C(7A)	1.519(3)
N(3A)-C(3A)	1.360(2)	C(7A)-C(8A)	1.519(3)
N(4A)-C(2A)	1.331(2)	C(5A)-H(5AB)	0.9900

Table 7. Bond angles in molecule **5a**.

Angle	φ (°)	Angle	φ (°)
C(1A)-O(1A)-C(4A)	117.40(12)	N(1A)-C(2A)-N(2A)	125.07(14)
C(1A)-N(1A)-C(2A)	113.09(12)	N(2A)-C(3A)-N(5A)	118.47(13)
C(3A)-N(2A)-C(2A)	114.82(13)	N(2A)-C(3A)-N(3A)	124.84(13)
C(1A)-N(3A)-C(3A)	113.36(13)	N(5A)-C(3A)-N(3A)	116.67(14)
C(3A)-N(5A)-C(9A)	122.72(13)	N(5A)-C(5A)-C(6A)	110.26(14)
C(3A)-N(5A)-C(5A)	122.60(13)	C(7A)-C(6A)-C(5A)	110.40(16)
C(9A)-N(5A)-C(5A)	114.40(12)	C(8A)-C(7A)-C(6A)	110.94(14)
N(3A)-C(1A)-N(1A)	128.57(14)	C(7A)-C(8A)-C(9A)	111.32(15)
N(3A)-C(1A)-O(1A)	118.66(14)	N(5A)-C(9A)-C(8A)	109.94(14)
N(1A)-C(1A)-O(1A)	112.77(13)	O(1A)-C(4A)-H(4AA)	109.5
N(4A)-C(2A)-N(1A)	117.49(13)	N(5A)-C(5A)-H(5AA)	109.6
N(4A)-C(2A)-N(2A)	117.45(13)		

Table 8. Hydrogen bonds for compound **5a** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(4A)-H(1N)...N(1A)#1	0.876(19)	2.185(19)	3.0578(19)	175.1(16)
N(4A)-H(2N)...N(1B)#2	0.911(19)	2.12(2)	3.0073(19)	162.8(16)
N(4B)-H(3N)...N(2B)#2	0.89(2)	2.44(2)	3.299(2)	161.3(17)
N(4B)-H(4N)...N(2A)#2	0.90(2)	2.17(2)	3.072(2)	178.0(17)

Symmetry transformations used to generate equivalent atoms: #1 -*x*+1, -*y*+1, -*z* #2 -*x*+1, -*y*+1, -*z*+1

Table 9. Selected interatomic distances in molecule **3a**.

Bond	d (Å)	Bond	d (Å)
O(2)-C(3)	1.2358(15)	N(6)-C(5)	1.3261(15)
N(1)-N(2)	1.2923(15)	N(6)-C(6)	1.3480(17)
N(1)-C(2)	1.3709(16)	N(7)-C(6)	1.3136(17)
N(2)-N(3)	1.3719(14)	N(7)-C(7)	1.3591(15)
N(3)-C(1)	1.3744(15)	N(8)-C(7)	1.3260(16)
N(3)-C(5)	1.4260(16)	N(8)-C(9)	1.4648(16)
N(4)-C(3)	1.3271(17)	N(8)-C(13)	1.4648(15)
N(5)-C(5)	1.3110(16)	C(1)-C(2)	1.3691(18)
N(5)-C(7)	1.3627(16)	C(1)-C(4)	1.4854(17)

Table 10. Bond angles in molecule **3a**.

Angle	φ (°)	Angle	φ (°)
C(6)-O(1)-C(8)	116.53(10)	N(6)-C(5)-N(3)	115.42(10)
N(2)-N(1)-C(2)	109.59(10)	N(7)-C(6)-O(1)	119.23(11)
N(1)-N(2)-N(3)	106.91(10)	N(7)-C(6)-N(6)	127.99(11)
N(2)-N(3)-C(1)	110.81(10)	O(1)-C(6)-N(6)	112.78(11)
N(2)-N(3)-C(6)	118.19(9)	N(8)-C(7)-N(7)	118.63(11)
N(2)-N(3)-C(5)	118.15(9)	N(8)-C(7)-N(5)	117.95(11)
C(1)-N(3)-C(5)	130.99(10)	N(7)-C(7)-N(5)	123.41(11)
C(5)-N(5)-C(7)	113.52(10)	N(8)-C(9)-C(10)	109.60(11)
C(6)-N(7)-C(7)	114.51(11)	C(9)-C(10)-C(11)	110.86(11)
C(7)-N(8)-C(9)	122.59(10)	C(12)-C(11)-C(10)	110.98(11)
C(7)-N(8)-C(13)	123.26(10)	C(13)-C(12)-C(11)	110.94(11)
C(9)-N(8)-C(3)	113.77(10)	N(8)-C(13)-C(12)	109.63(11)
C(2)-C(1)-N(3)	103.27(10)	O(2)-C(3)-N(4)	124.10(12)
N(3)-C(1)-C(4)	126.63(11)	O(2)-C(3)-C(2)	120.96(12)
C(1)-C(2)-N(1)	109.42(11)	N(4)-C(3)-C(2)	114.94(11)
C(1)-C(2)-C(3)	129.34(11)	N(5)-C(5)-N(6)	129.76(12)
N(1)-C(2)-C(3)	121.18(11)	N(5)-C(5)-N(3)	114.82(10)

Table 11. Hydrogen bonds for compound **3a** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(4)-H(1N)...N(1)#1	0.884(17)	2.248(18)	3.0693(16)	154.5(14)
N(4)-H(2N)...O(1W)#2	0.888(18)	2.100(18)	2.9559(16)	161.7(15)
O(1W)-H(1W)...O(2)	0.88(2)	1.98(2)	2.8598(14)	173.5(19)
O(1W)-H(2W)...N(6)#3	0.85(2)	2.39(3)	3.2187(15)	165(2)

Symmetry transformations used to generate equivalent atoms: #1: *-x, -y*+1, -z; #2: *-x, -y, -z;* #3: *x, y*-1, *z.*

^{1}H NMR spectra of all synthesized compounds had expected signals of all corresponding protons and the integration curves prove the ratios of these protons (Table 1). The protons of the amide group had a singlet signal in the area of 8.03-9.28 ppm for the compounds **3a-r** and in the area 5.18-5.52 ppm for the compounds **4a-c**. It is interesting that N-H protons of amino group in compounds **4a-c** were observed in the area of 6.81-7.18 and 13.51-12.72 respectively. This unusual splitting can be explained by strong intramolecular hydrogen bonding between one of the NH_2 protons and one of the nitrogen atoms in triazine ring. The amino group protons in compounds **5a-c** exhibited a broad singlet signal in the area of 4.65-4.96 ppm [24].

The mass spectroscopic molecular ions were observed in the spectra of compounds **3a-r**, **4a-c** and **5a-c**, which further confirmed their structure. Compounds **3d**, **3g**, **4b**, and **5a-c** displayed the maximum intensity of the molecular ions. The fragmentation patterns of the molecular ions under electron impact were found to be the same as it was observed for the earlier synthesized heterocyclic derivatives of the 1,3,5-triazine [8,11,25].

To study the fine structure of the resulting triazolyl-triazines, we carried out X-ray diffraction for compounds **3a** and **3r** whose crystals were grown from an iso-propanol/water mixture. The projection of the three-dimensional structure of the derivatives **3a** and **3r** are shown in Figure 1 and 5. Selected interatomic distances and bond angles are given in Table 3-8 and Table 9-11, respectively. The complete tables of aromatic coordinates, thermal parameters, bond lengths, and bond angles were deposited with the Cambridge Structural Database.

In summary, a series of new 1,3,5-triazine derivatives containing the 1,2,3 triazole moiety were synthesized and the synthetic methods were optimized. Two different reaction conditions were investigated. We found that using triethylamine as a catalyst and DMF as a solvent in a reaction between 2-azido-4,6-disubstituded-1,3,5-triazines and methylene-active dicarbonyl compounds under room temperature conditions smoothly leads to the triazolyl derivatives of 1,3,5-triazine with good yields. The reaction between azido-triazine and cyanoacetomide under the same conditions and heating up to 60 °C leads to the formation of 1,2,3-triazolyl-1,3,5-triazines. At the same time, the reaction between azido- derivatives and cyanoacetamide under super basic conditions and heating produced two products, the triazolyl derivatives and the other unexpected 2-amino-4,6-disubstituted-1,3,5-triazines. Fine structures of the 1,3,5-triazines connected with 1,2,3-triazole ring and amino-triazines was studied on the example of compounds **3r**, **3a** and **5a** (Figure 1, 3 and 5).

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Supplementary data

CCDC 859327 (Compound **3a**), CCDC 859328 (Compound **3r**) and CCDC 859326 (Compound **5a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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