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Synthesis of new 4,6-disubstituted-1,3-5-triazin-2-yloxy esters and *N*-hydroxyamides

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ABSTRACT

A convenient method for synthesis of new sym-triazine ester and hydroxamate derivatives has been developed. Various reaction conditions were studied and optimized, and a series of new 1,3,5-triazine based esters and *N*-hydroxyamides were obtained with good yields (38-80%). The reaction between oxo-derivatives of 4,6-disubstituted-1,3,5-triazines and halogenated carboxylic esters derivatives using Cs_2CO_3 as a catalyst was found to be the most convenient method for 4,6-disubstituted-1,3,5-triazine-2-yloxy esters synthesis. These 1,3,5-triazin based esters served as precursors for the synthesis of 4,6-disubstituted-1,3,5-triazin-2-yloxy-*N*-hydroxybutanamides using solution of hydroxylamine hydrochloride in dry methanol and KOH at room temperature. Structures of the newly synthesized compounds were obtained by ^{1}H NMR, ^{13}C NMR, MS, IR spectral data and elemental analysis.

1. Introduction

Hydroxamic acids (HA) were discovered by Hoffman in 1889 [1] and till this day their high biological activity and practical value [2-6] attract the interest of many researchers. Hydroxamic acids are good chelators and widely used in analytical chemistry [4]. HA can also be used for fishing out heavy and transition metals from diluted solutions of their salts [7,8]. However, the biggest attraction to the chemistry of hydroxamic acids is due their high biological activity [9-16] such as inhibitors for different enzymatic systems [9,10], carcenolytics [11-13], killers against plant-parasitic in various organisms [14,15], as well as very active antimalarial compounds [16].

Furthermore, 1,3,5-triazine derivatives posses a wide variety of biological activity as HIV treatment, and as catalysts, herbicides, carcenolytics [17-20], as well as compounds with growth-stimulating activity, antidote activity, nontoxic cationic surfactants, and inhibitors of the oil oxidizing processes [21-28].

Combination of these two bioactive moieties in one structure could enhance their existing bioactivities. Synthesis and investigation of some physical properties of new hydroxamic acids containing the sym-triazine backbone (THA) was the subject of our interest in this research.

Hydroxamic acids can be synthesized from amino acids and hydroxyl amine using cyanuric chloride acid as a catalyst [29]. The most common method of HA synthesis is treating the ester derivatives with hydroxyl amine [12,30-35]. Although some sym-triazine containing esters have been described, which were synthesized through a multistep synthesis using melamine and isocyanates [30], only one article was found where the sym-triazine based hydroxamic acids have been described [31]. The initial reagent for the synthesis of these THA was melamine and these hydroxamic acids have been used for the investigation of the gel formation processes [31].

Both methods [30,31] allow synthesis of only α-amino acid ester, amide, or hydroxamate derivatives of sym-triazines. The syntheses of hydroxamates of oxy-acid derivatives of sym-triazines have not been previously described.

2. Experimental

2.1. Instrumentation and materials

The IR spectra were recorded on a BRUKER-Alpha P spectrophotometer. The ^{13}C and ^{1}H NMR spectra of esters and hydroxamates 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.

The initial 2,4-disubstituted-6-chloro-1,3,5-triazines, starting ammonium salts (I) and oxocompounds (II) were prepared from cyanuric chloride according to the procedures described earlier [2, 7, 36, 37]. The solvents have been purified and dried according to the procedures as described earlier [38, 39].

2.2. Synthesis

2.2.1. Compounds III a-k

Compounds **III a-k** were synthesized similarly. *Ethyl 4-(4,6-dimorpholino-1,3,5-triazine-2-yloxy)butanoate* (**IIIh**): 1.337g

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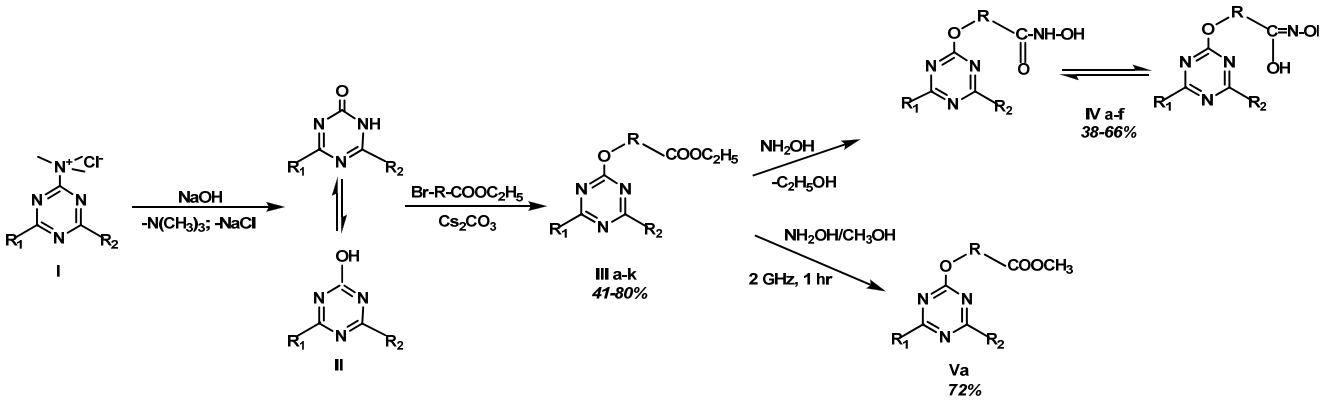
Table 1. IR, NMR and Mass Spectra of new esters and hydroxamic acids–1,3,5-triazine derivatives.

Compound	IR-spectrum, ν(cm^{-1})	^{1}H NNR δ (*ppm*)	^{13}C NMR δ (*ppm*)	MS *m/z* (I_{rel}, %)
IIIa	1728 (C=O); 1604; 1568; 1530 (–C=C + -C=N); 1263 (-C-N); 1160 ; 1123 ; 1084 ; 1008 (C–O-C)	4.80 (2H, s, O**CH$_2$**CO); 4.16 (2H, q, J=6, O**CH$_2$**CH$_3$); 3.72 (8H, t, J=6, Σ 2N-**CH$_2$**); 1.67-1.59 (4H, m, **CH$_2$** piperid.); 1.57-1.49 (8H, m, **CH$_2$** piperid.); 1.24 (3H, t, J=6, OCH$_2$**CH$_3$**)	178.4, 174.4, 169.3, 65.5, 61.3, 52.4, 25.9, 25.5, 14.1	349(65)
IIIb	1744 (C=O); 1582, 1539; 1496 (–C=C + -C=N); 1255 (-C-N); 1155, 1107; 1063; 1001 (C-O-C)	4.74 (2H, s, O**CH$_2$**CO); 4.20 (2H, q, J=6, O**CH$_2$**CH$_3$); 3.79 (8H, t, J=6, Σ 2N-**CH$_2$**); 3.64 (8H, t, J=6, Σ O**CH$_2$**CH$_2$N); 1.25 (3H, t, J=6, OCH$_2$ **CH$_3$**)	178.8, 176.5, 169.3, 66.4, 65.4, 62.2, 46.3, 15.5	353(77)
IIIc	3081, 2976 (CH Ph); 1754 (C=O); 1590, 1553, 1499 (–C=C + -C=N); 1195; 1134; 1069; 1020 (C-O-C)	7.44-7.34, 7.32-7.22, 7.21-7.11 (10H, m, Σ**CH** OPh); 4.98 (2H, s, O**CH$_2$C=O**); 4.23 (2H, q, J=5.4; O**CH$_2$**CH$_3$); 1.29 (3H, t, J=5.4; OCH$_2$**CH$_3$**)	181, 174.6, 168.5, 155.2, 129.8, 124.7, 121.3, 65.6, 62.5, 18.5	367(100)
IIId	1578, 1530; 1498 (–C=C +–C=N); 1269 (C-N); 1174, 1118, 1083, 1022 (C-O-C)	4.31 (2H, t, J=6.0; O**CH$_2$** (CH$_2$)$_2$CO); 4.13 (2H, q, J=6; O**CH$_2$**CH$_3$); 3.72 (8H, t, Σ2**CH$_2$**N-**CH$_2$**); 2.47 (2H, t, J=6.0; **-CH$_2$**C=O); 2.16 (2H, t.t.; J=6; OCH$_2$**CH$_2$**CH$_2$); 1.68-1.59 (4H, m, **CH$_2$** piperid.); 1.58-1.49 (8H, m, **CH$_2$** piperid.); 1.21 (3H, t, J=6, OCH$_2$**CH$_3$**)	178.4, 171.4, 122.8, 70.4, 65.5, 49.7, 36.1, 31.1, 30.09, 29.9, 19.1	377(65)
IIIe	1744 (C=O); 1587, 1538, 1504 (–C=C + -C=N); 1165, 1122 , 1089, 1017 (C-O-C)	4.43 (2H, t, J=6.3; **CH$_2$** (CH$_2$)$_2$CO); 4.11 (2H, q, J=6.3; O**CH$_2$**CH$_3$); 3.91 (6H, s, O**CH$_3$**); 2.53 (2H, t, J=6.3; **-CH$_2$**C=O); 2.21 (2H, t.t.; J=6.3; OCH$_2$**CH$_2$**CH$_2$); 1.23 (3H, t, J=4.8; OCH$_2$**CH$_3$**)	177.9, 175.7, 170.7, 70.03, 65.3, 45.8, 36.1, 19.4	71(60)
IIIf	1732 (C=O); 1580, 1528, 1501 (–C=C + –C=N); 1252 (-C-N); 1180, 1109, 1049, 1006 (C-O-C)	4.40 (2H, t, J=5.4; O**CH$_2$** (CH$_2$)$_2$); 4.14 (2H, q, J= 5.4; O**CH$_2$**CH$_3$); 3.94 (3H, s, O**CH$_3$**); 3.86 (4H, t, J=5.4; Σ N**CH$_2$**); 3.71 (4H, t, J=5.4; O**CH$_2$**); 2.50 (2H, t, J=5.4; **CH$_2$**CO); 2.15-2.06 (2H, m, COCH$_2$ **CH$_2$**); 1.25 (3H, t, J=5.4; OCH$_2$**CH$_3$**)	182, 173.5, 173.1, 169.8, 68.3, 66.3, 61.2, 55.8, 46.5, 30.1, 24.5, 19.2	326(68)
IIIg	3062, 2961 (CH Ph); 1727 (C=O); 1598, 1562, 1497 (C=C + C=N); 1163, 1125, 1091, 1021 (C-O-C)	7.45-7.35, 7.28-7.19, 7.18-7.10 (10H, m, Σ **CH**OPh); 4.33 (2H, t, J=6.0; O**CH$_2$** (CH$_2$)$_2$CO); 4.12 (2H, q, J=6.0; O**CH$_2$**CH$_3$); 2.53 (2H, t, J=6.0; **-CH$_2$**CO); 2.09-2.00 (2H, m, OCH$_2$**CH$_2$**CH$_2$); 1.30 (3H, t, J=6.0; OCH$_2$**CH$_3$**)	179.1, 178.1, 157.5, 135.1, 131.6, 127.1, 122.8, 73.2, 65.7, 35.7, 29.2, 19.1	395(86)
IIIh	1728 (C=O); 1574, 1531, 1498 (C=C + C=N); 1251 (-C-N); 1183, 1115, 1047, 1021 (C-O-C)	4.32 (2H, t, J=6.0; O**CH$_2$**CH$_2$CH$_2$); 4.14 (2H, q, J= 6.0; O**CH$_2$**CH$_3$); 3.80 (8H, t, J=6.0; ΣO**CH$_2$**); 3.68 (8H, t, J= 6.0; N**CH$_2$**CH$_2$O); 2.46 (2H, t, J=6.0; **CH$_2$**CO); 2.15-2.06 (2H, m, CH$_2$**CH$_2$**CH$_2$CO); 1.23 (3H, t, J=6.0; OCH$_2$**CH$_3$**)	178.5, 175.4, 172.9, 68.4, 66.9, 61.6, 47.1, 30.3, 24.4, 18.9	381(57)
IIIi	1736 (C=O); 1591, 1523, 1499 (–C=C + C=N); 1284 (CN); 1174, 1129, 1105, 1030 (C-O-C)	4.35 (2H, t, J=5.5; O**CH$_2$** (CH$_2$)$_2$); 4.11 (2H, q, J= 5.5; O**CH$_2$**CH$_3$); 3.96 (3H, s, O**CH$_3$**); 3.79-3.71 (4H, m, ΣN**CH$_2$**); 2.46 (2H, t, J=5.5; CO**CH$_2$**); 2.12-2.03 (2H, m, OCH$_2$**CH$_2$**CH$_2$); 1.68-1.61 (2H, m, **CH$_2$**piperid.) 1.59-1.52 (4H, m, **CH$_2$**piperid.); 1.23 (3H, t, J=5.5; OCH$_2$**CH$_3$**)	181.7, 173.3, 173.1, 169.5, 68.5, 62.5, 56.1, 52.4, 30.7, 25.9, 25.5, 24.6, 20.4	324(71)
IIIj	1731 (C=O); 1574, 1529, 1498 (C=C + C=N); 1256 (CN); 1158, 1111, 1095, 1034 (C-O-C)	4.32 (2H, t, J=5.8; O**CH$_2$**CH$_2$); 4.12 (2H, q, J= 5.8; O**CH$_2$**CH$_3$); 3.95 (3H, s, O**CH$_3$**); 3.84 (4H, t, J=5.8 Σ N**CH$_2$**); 3.72 (4H, t, J=5.8; ΣO**CH$_2$**); 2.32 (2H, t, J=5.8; **CH$_2$**CO); 1.85-1.76 [2H, m, OCH$_2$**CH$_2$** (CH$_2$)$_3$]; 1.73-1.64 (2H, m, O (CH$_2$)$_3$ **-CH$_2$**); 1.53-1.44 (2H, m, O (CH$_2$)$_2$**CH$_2$** (CH$_2$)$_2$ CO); 1.26 (3H, t, J=5.4; OCH$_2$**CH$_3$**)	178.8, 176.5, 171.8, 122.8, 71.8, 71.5, 49.1, 39.2, 35.4, 33.8, 30.7, 29.9, 19.1	354(60)
IIIk	3063, 2978 (CHPh); 1730 (C=O); 1596, 1553, 1499 (-C=C + –C=N); 1162, 1115, 1081, 1029 (C-O-C)	7.44-7.34, 7.28-7.18, 6.96-6.86 (10H, m, Σ**CH**OPh); 4.13 (2H, q, J=6.0; O**CH$_2$**CH$_3$); 3.95 (2H, t, J=6.0; O**CH$_2$**CH$_2$); 2.36 (2H, t, J=6.0; **CH$_2$**CO); 1.84-1.75 (2H, m, OCH$_2$**CH$_2$** (CH$_2$)$_3$CO); 1.59-1.50 (2H, m, O (CH$_2$)$_3$**CH$_2$** CH$_2$CO); 1.43-1.34 (2H, m, OCH$_2$CH$_2$**CH$_2$** CH$_2$ CH$_2$CO); 1.27 (3H, t, J=6.0; OCH$_2$**CH$_3$**)	181.7, 173.3, 173.1, 169.5, 68.9, 66.4, 62.5, 55.8, 46.9, 33.9, 29.5, 25.9, 20.4	423(45)
IVa	3204 (O-H, N-H); 1672(C=Oamid); 1576, 1515, 1499 (C=C + C=N); 1251 (C-N); 1202, 1114, 1067, 1004 (C-O-C)	8.22 (1H, s, HO-**NH**); 4.75 (2H, s, O**CH$_2$**CO); 3.77 (8H, t, J=3.0; ΣN**CH$_2$**CH$_2$O); 3.68 (8H, t, J=3.0; Σ O**CH$_2$**CH$_2$N); 1.78 (1H, s, **HO**-NH)	170.1, 168.2, 166.1, 66.6, 44.1, 40.6	340(38)
IVb	3258 (O-H, N-H); 1693 (C=Oamid); 1567, 1528, 1497 (C=C + C=N); 1250 (CN); 1163, 1107, 1047, 1008 (C-O-C)	8.36 (1H, s, HO-**NH**); 4.34 (2H, t, J=4.0; O**CH$_2$** (CH$_2$)$_2$CO); 3.78 (8H, t, J=4.0; ΣN**CH$_2$**); 3.70 (8H, t, J=4.0; ΣO**CH$_2$**); 2.46 (2H, t, J=4.0; **CH$_2$**CO); 2.18 (1H, s, **HO**-NH); 2.13-2.04 (2H, m, OCH$_2$**CH$_2$**CH$_2$)	170.9, 169.2, 165.9, 67.9, 66.4, 44.3, 31.4, 24.9	368(53)
IVc	3274 (O-H, N-H); 1688 (C=Oamid); 1577, 1532, 1498 (C=C + C=N); 1239 (CN); 1154, 1122, 1049, 1006 (C-O-C)	8.43 (1H, s, HO-**NH**); 4.34 (2H, t, J=4.8; O**CH$_2$** (CH$_2$)$_2$CO); 3.97 (3H, s, O**CH$_3$**); 3.71 (8H, t, J=4.8; Σ N-**CH$_2$**CH$_2$O); 3.71 (8H, t, J=4.8; ΣO**CH$_2$**CH$_2$N); 2.49 (2H, t, J=4.8; **-CH$_2$**CO); 2.48 (1H, s, **HO**-NH); 2.13-2.04 (2H, m, OCH$_2$**CH$_2$**CH$_2$)	182, 173.1, 169.9, 67.9, 66.4, 55.8, 46.4, 28.8, 25.0	327(100)
IVd	3041, 2811 (CH Ph); 1696 (C=Oamid); 1570, 1548, 1498 (C=C + C=N); 1169, 1115, 1060, 1010 (C-O-C)	8.42 (1H, s, HO-**NH**); 7.57-7.47 , 7.38-7.28, 7.22-7.12 (10H, m, Σ**CH**OPh); 4.33 (2H, t, J=5.1; O**CH$_2$**CH$_2$CH$_2$CO); 2.53 (2H, t, J=5.1; **CH$_2$**CO); 2.29 (1H, s, **HO**-NH); 2.08-2.00 (2H, m, OCH$_2$**CH$_2$**CH$_2$)	181, 174.5, 169.8, 155.2, 129.8, 124.8, 121.3, 68.2, 27.9, 24.8	410(48)
IVe	3239 (O-H, N-H); 1703 (C=Oamid); 1594, 1562; 1496 (C=C + –C=N); 1239 (CN); 1186, 1118, 1047, 1011 (C-O-C)	8.51 (1H, s, HO-**NH**); 4.11 (2H, t, J=6.0; O**CH$_2$**CH$_2$CH$_2$CO); 3.16 (8H, t, Σ**CH$_2$**N); 2.48 (1H, s, **HO**-NH); 2.27 (2H, t, J=6.0; **-CH$_2$**C=O); 2.14-2.06 (2H, m , OCH$_2$**CH$_2$**CH$_2$); 1.58-1.49 (4H, m, **CH$_2$** pypired.); 1.51-1.42 (8H, m, **CH$_2$** pypired.)	178.6, 173.5, 170.2, 67.7, 52.4, 28.8, 26.1, 25.5, 25.0	364(78)
IVf	3220 (O-H, N-H); 1684 (C=Oamid); 1561, 1531, 1498 (C=C + C=N); 1247 (C-N); 1193, 1150, 1106, 1002 (C-O-C)	8.12 (1H, s, HO-**NH**); 4.27 (2H, t, J=6.3; O**CH$_2$**CH$_2$); 3.55 (8H, t, J=6.3; ΣN**CH$_2$**); 3.46 (8H, t, J=6.3; Σ O**CH$_2$**); 2.40 (2H, t, J=6.3; **CH$_2$**CO); 2.09 (1H, s, **HO**-NH); 1.83-1.75 (2H, m, OCH$_2$**CH$_2$** (CH$_2$)$_3$CO); 1.74-1.65 (2H, m, O (CH$_2$)$_3$**CH$_2$**CH$_2$CO); 1.53-1.44 (2H, m, OCH$_2$CH$_2$-**CH$_2$**CH$_2$CH$_2$CO)	173.9, 173.5, 171.0, 66.6, 66.3, 40.6, 33.8, 29, 25.7, 25.0	396(61)

Table 2. Characteristics of Synthesized compounds **IIIa-k**, **IVa-f, Va**.

Compound	Empirical formula	Found (Calculated) (%)			M.p. (°C)	Yield (%)
		C	H	N		
IIIa	$C_{17}H_{27}N_5O_3$	58.23 (58.43)	8.02 (7.79)	20.29 (20.04)	84-86	52.7
IIIb	$C_{15}H_{23}N_5O_5$	51.17 (50.98)	6.41 (6.56)	19.66 (19.82)	90-92	73.0
IIIc	$C_{19}H_{17}N_3O_5$	62.25 (62.12)	4.52 (4.66)	11.60 (11.44)	75-78	47.3
IIId	$C_{19}H_{31}N_5O_3$	60.58 (60.45)	8.41 (8.28)	18.63 (18.55)	60-62	68.0
IIIe	$C_{11}H_{17}N_3O_5$	48.53 (48.70)	6.47 (6.32)	15.67 (15.49)	76-78	48.4
IIIf	$C_{14}H_{22}N_4O_5$	55.37 (55.52)	6.58 (6.79)	17.29 (17.17)	40-42	59.7
IIIg	$C_{21}H_{21}N_3O_5$	63.64 (63.79)	5.51 (5.35)	10.52 (10.63)	70-72	50.8
IIIh	$C_{17}H_{27}N_5O_5$	53.45 (53.53)	4.28 (4.14)	18.49 (18.36)	73-75	69.2
IIIi	$C_{15}H_{24}N_4O_4$	55.66 (55.54)	7.58 (7.45)	17.39 (17.27)	38-40	40.1
IIIj	$C_{16}H_{24}N_4O_5$	54.36 (54.22)	7.19 (7.39)	15.95 (15.81)	34-36	41.2
IIIk	$C_{23}H_{25}N_3O_5$	65.38 (65.21)	5.84 (5.95)	9.83 (9.92)	62-65	49.5
IVa	$C_{13}H_{20}N_6O_5$	45.69 (45.88)	5.78 (5.92)	24.76 (24.69)	146-148	47.9
IVb	$C_{15}H_{24}N_6O_5$	48.45 (48.90)	6.28 (6.57)	22.98 (22.81)	158-160	54.1
IVc	$C_{13}H_{21}N_5O_5$	47.76 (47.64)	6.58 (6.49)	21.19 (21.40)	150-153	41.5
IVd	$C_{20}H_{20}N_4O_5$	58.41 (58.53)	5.04 (4.91)	17.21 (17.06)	140-141	46.3
IVe	$C_{17}H_{28}N_6O_3$	56.18 (56.03)	7.84 (7.74)	23.18 (23.06)	179-180	38.4
IVf	$C_{17}H_{28}N_6O_5$	51.36 (51.50)	7.29 (7.12)	21.35 (21.20)	182-183	65.9
Va	$C_{16}H_{25}N_5O_5$	52.03 (52.25)	6.97 (6.80)	19.36 (19.05)	101-103	72.1



IIIa,d $R_1 = R_2$ = Piperidino, R = CH_2 **IIIa**, $(CH_2)_3$ **IIId**; **IIIb,h Va** $R_1 = R_2$ = Morpholino, R = CH_2 **IIIb, Va**; $(CH_2)_3$ **IIIh, IIIf,j** $R_1 = OCH_3$, R_2 = Morpholino, R = $(CH_2)_3$ **IIIf,** $(CH_2)_5$ **IIIj**; **IIIc,g,k** $R_1 = R_2 = OC_6H_5$, R = CH_2 **IIIc,** $(CH_2)_3$ **IIIg,** $(CH_2)_5$ **IIIk**; **IIIe** $R_1 = R_2 = OCH_3$, R = $(CH_2)_3$; **IIIi** $R_1 = OCH_3$, R_2 = Piperidino, R = $(CH_2)_3$; **IVa,b,f** $R_1 = R_2$ = Morpholino, R = CH_2 **IVa,** $(CH_2)_3$ **IVb,** $(CH_2)_5$ **IVf**; **IVc** $R_1 = OCH_3$, R_2 = Morpholino, R = $(CH_2)_3$; **IVd** $R_1 = R_2 = OC_6H_5$, R = $(CH_2)_3$; **IVe** $R_1 = R_2$ = Piperidino, R = $(CH_2)_3$.

Figure 1. Synthesis of the (2,4-disubstituted-1,3,5-triazin-2-yloxy)-*N*-hydroxyamides and esters.

(4.99 mmol) of 4,6-dimorpholino-1,3,5-triazin-2(1H)-one was dissolved in 15 mL of dry DMF at 60 °C and stirred for 10 min and then the solution of 1.114 g (4.99 mmol) ethyl 4-bromobutanoate and 1.735 g (5.49 mmol) Cs_2CO_3 in 15 mL DMF was added drop wise. The reaction mixture was stirred at 60-80 °C for 4 hours. Progress of the reaction was monitored by TLC. The solution was allowed to cool down to 20 °C and 25 mL of ice cold water was added with continued stirring. The reaction mixture was kept on an ice bath approximately 2-3 hour to ensure that maximum amount of white precipitate was obtained. The product was filtered and washed out with cold water (3 x 20 mL) and dried at 50 °C. After purification by crystallization from ethanol:water solution (3:2), 1.316 g of compound **IIIh** was obtained (69.2%) (Figure 1). Physico-chemical characteristics of synthesized compounds could be found in Table 1 and 2.

2.2.2. Compounds IV a, c-f

Compounds **IV a, c-f** were prepared similarly. *4-(4,6-Dimorpholino-1,3,5-triazin-2-yloxy)-N-hydroxybutanamide* (**IVb**)**:** A solution of 0.639 g (9.2 mmol) hydroxylamine hydrochloride in 10 mL of dry methanol and 0.515 g (9.2 mmol) KOH in 10 mL dry methanol were mixed at room temperature. The reaction mixture was stirred in an ice bath for 10 min and filtered. The resulting solution was slowly added to a solution of 1.16 g (3.045 mmol) of ethyl 4-(4,6-dimorpholino-1,3,5-triazine-2-yloxy)butanoate in 25 mL of dry methanol. The reaction mixture was refluxed for 6 hours and progress of the reaction was monitored by TLC. The solution was allowed to cool down to 20 °C. The reaction mixture was evaporated by vacuum. The resulting residue was dried at 50 °C and purified by crystallization from *iso*-propanol:water (3:1) solution (Figure 1). The final yield was 0.606 g (54.1%). Physico-chemical characteristics of synthesized compounds could be found in Table 1 and 2.

2.2.3. Compounds Va

Methyl 4-(4,6-dimorpholino-1,3,5-triazine-2-yloxy)butanoate (**Va**): A solution of 0.639 g (9.2 mmol) hydroxylamine hydrochloride in 10 mL of dry methanol and 0.515 g (9.2 mmol) KOH in 10 mL dry methanol were mixed at room temperature. The reaction mixture was stirred in an ice bath for 10 min and filtered. The resulting solution was slowly added to a solution of 1.16 g (3.045 mmol) of ethyl 4-(4,6-dimorpholino-1,3,5-triazine-2-yloxy)butanoate in 25 mL of dry methanol. The reaction mixture was heated in microwave at 2 GHz for 1 hour and progress of the reaction was monitored by TLC. The solvent was evaporated by vacuum. The product was filtered and washed out with cold water (3 x 20 mL) and dried at 50 °C. After purification by crystallization from ethanol: water solution (3:2), 0.83 g of compound **Va** was obtained (72%) (Figure 1). Physico-chemical characteristics of synthesized comp-ound could be found in Table 1 and 2.

3. Results and discussion

We investigated several different methods to synthesize the desired THA as shown in Figure 1. The attempts to synthesize

hydroxamates from sym-triazine carboxylic acids were not successful even using cyanuric chloride as a catalyst. This method is also not very suitable due to the limited number of hydroxyl containing acids available. It was possible to synthesize THA using esters **III** as intermediate compounds. This could be achieved using 4,6 disubstituted-2-(trimethylamino) chlorides **I** as initial compounds [36,37]. Unfortunately, the attempts to synthesize esters **III** with direct reaction between quaternary salts **I** and some esters of oxycarboxylic acids were not successful probably due to the relatively low nucleophilicity of the hydroxy group in these acids. Salts hydrolysis products **(II)** were the major products in all of these cases. We found that alkylation of oxo-derivatives **II** is the most convenient and successful method for the esters **(III)** synthesis. Compounds **II** could be easily synthesized by the basic hydrolysis of quaternary salts [36].

The progress of the reactions was monitored using TLC. It is interesting to note that the alkylation of the oxo-derivatives **II** with the ω-bromo-alkenylesters in the presence of equimolar amounts of KOH, NaOH, or K_2CO_3 as acceptors of HBr takes about several days to complete with very low yields (10-15 %). Increasing the reaction time, as well as using different types of purified protic solvents [38,39] did not affect the final product yields. Alternatively, using dry DMF as a solvent and equimolar amount of Cs_2CO_3 as a base have been found to be optimal conditions for this synthesis. This helped to increase the final yields to 39-80% (see Table 1) as well as decrease the reaction time from few days to several hours.

The sym-triazine ester derivatives **(III)** were treated with three equivalents of freshly prepared hydroxyl amine in dry methanol to produce the final products [12,32-35]. The final yields under these conditions were 38-66%. Attempts to increase the final product's yield using KCN [34] as a catalyst or microwave conditions [12] were not very successful. The main product of reaction between compound **IIIh** and hydroxylamine using dry methanol as a solvent under microwave synthesis conditions was transesterefication product **Va.** Using THF as a solvent for microwave synthesis did not produce the desired product with a reasonable yield.

The new compounds **III** and **IV** are white or light yellow crystals. They are not soluble in water and alkanes; **THA** have a good solubility only in dioxane, DMF, DMSO, and other organic solvents with a high boiling point; esters are soluble in alcohols, dichloromethane, and chloroform. Compounds **III** have lower melting points (34-95 °C) compared with compounds **IV** (140-182 °C), as expected, due to the absence of the hydrogen bonds. The melting point values for both types of sym-triazine derivatives were lower with longer carbon chain length.

The structures of all synthesized compounds established by IR, ^{13}C NMR, ^{1}H NMR, Mass-spectroscopy, and Elemental analysis data (see Tables 1, 2).

IR-spectroscopy peaks for compounds **III** and **IV** show variable intensity, with broad absorption bands as well as stretching vibrations typical for the functional groups in their structures. Compounds **III** and **IV** have three medium and strong absorption bands in the area 1603–1496 cm^{-1} typical for the conjugated C=C and C=N. The C=O singlet absorption band is seen for compounds **III** present at 1729-1760 cm^{-1}, while this signal has been shifted to higher frequencies (1703-1672 cm^{-1}) in case of THA. This is typical for the $C=O_{amid}$. Compounds **III** and **IV** all have four absorption bands at 1195-1002 cm^{-1} typical for the C-O-C functional group. IR spectra of compounds **IIIc, IIIg** and **IIIk** have medium and small absorption bands at 815-806 and 787–773 cm^{-1} typical for the bending vibrations of the γ_{CH} in Ph.

^{1}H NMR spectra data of all synthesized compounds have signals of all corresponding protons and the integration curves prove the number of protons. The single proton of the NH amide has a signal in the area of 8.12-8.51 ppm. Compounds **IV** have the singlet signal of the OH-NH group at 1.78-2.48 ppm, which is the most prominent structural distinction between these compounds. The protons of the morpholyl and piperidyl rings of derivatives **III** and **IV** appear as multiplet signals (see Table 1).

The mass spectroscopy spectra of compounds **III** and **IV** also confirm their structure. Compounds **IIIc** and **IVc** have the maximum intensity of the molecular ions. The fragmentation pattern of the molecular ions under electronic impact is the same as has been observed for the synthesized heterocyclic derivatives of the 1,3,5-triazine [36,37,40-43].

In summary, a series of new organic compounds containing ester and hydroxamate derivatives of 1,3,5-triazine have been prepared. The alkylation of sym-triazine oxo-derivatives was found to be the most convenient and successful method for the oxy-acid esters with triazine backbone. Treatment of these esters with freshly prepared hydroxylamine in methanol successfully lead to the new hydroxamate derivatives of 1,3,5-triazine. The investigation of the practical bioactivity of these derivatives is the subject for our future research.

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References

[1]. Knuniants I. Chem. Encyclopedia, 5th edition, *v. 1,* Sovietskaya encyclopedia Publishing House, Moscow, 1988.
[2]. Fazary, A. E.; Khalil, M. M.; Fahmy, A.; Tantawy, T. A. *Medical Journal of Islamic Academy of Sciences,* **2001**, *14(3)*, 109-116.
[3]. Dooley, C. M.; Devocelle, M.; McLoughlin, K. B.; Nolan, K. B.; Fitzgerald, D. J.; Sharkey, C. T. *Mol. Pharmacol.* **2003**, *63(2)*, 450-455.
[4]. Nigović, B.; Kujundžić, N.; Sanković, K.; Vikić-Topić, D. *Acta Chim. Slov.* **2002**, *49(3)*, 525-535.
[5]. Nirmal, K.; Huber, V.; Smith, P.; Gopalan, A. *Tetrahedron,* **1994**, *50(9)*, 2657-2664.
[6]. Huang, L.; Pardee, A. B. *Mol. Medicine,* **2000**, *6(10)*, 849-866.
[7]. Taylor, R. *Czech. J. Phys.* **1999**, *49*, 617-623.
[8]. Matijevic, J.; Samarzija, I.; Honovic, L.; Jurisic, B. *Acta Pharm*. **2008**, *58*, 231-236.
[9]. Kobashi, K.; Takebe, S.; Terashima, N.; Hase, J. *J. Biochem.* **1975**, *77*, 837-843.
[10]. Mishra, H.; Parrill, A. L.; Williamson, J. S. *Antimicrob. Agents Chemother*. **2002**, *46(8)*, 2613-2618.
[11]. Emanuele, S.; Lauricella, M.; Tesoriere, G. *Int. J. Oncol.* **2008**, *33(4)*, 637-646.
[12]. Massaro, A.; Mordini, A.; Reginato, G.; Russo, F.; Taddei M. *Synthesis.* **2007**, *20*, 3201-3204.
[13]. Ning, L.; Greenblatt, D. Y.; Kunnimalaiyaan, M.; Chen, H. *Oncologist*, **2008**, *13(2)*, 98-104.
[14]. Niemeyer, H. M. *Euphytica*, **1988**, *37(3)*, 289-293.
[15]. Zasada, I.; Meer, S.; Halbrendt, J.; Rice C. *Nematology*, **2005**, *95*, 1116-1121.
[16]. Holland, K. P.; Elford, H. L.; Bracchi, V.; Annis, C. G.; Schuster, S. M.; Chakrabarti, D. *Antimicrob. Agents Chemother.* **1998**, *42(9)*, 2456-2458.
[17]. Blotny, G. *Tetrahedron*, **2006**, *62(41)*, 9507-9522.
[18]. Smolin, E.; Rappoport, L. s-Triazine and Derivatives, Interscience, NY, 1959.
[19]. Melnikov, N.; Bascakov, Y. Chemistry of Herbicides and Growth Regulators of Plants, Goskhimizdat Publishing House, Moscow, 1962.
[20]. Pogosian, G.; Pankratov, V.; Zaplishny, V.; Matsoyan, S.; Korshak, V. Polytriazines, Armenian SSR Academy of Sciences Publishing House, Erevan, 1987.
[21]. Katritzky, A.; Rees, C.; Scriven, E.; Potts, K. Comprehensive Heterocyclic Chemistry, v. 5, Pergamon, Oxford, 1984.
[22]. Demirayak, S.; Karaburun, A. C.; Beis R. *Eur. J. Med. Chem.* **2004**, *39(12)*, 1089-1095.
[23]. Antonian, S.; Zaplishny, V.; Pogosian, G.; Libinzon, R.; Lavretskaya, E.; Pijov, V.; Bessudnova, N.; Sarkisian, D.; Vatolkina O. *Khimiko-Farmatsevticheskii Zhurnal* **1986**, *20(2),* 172-175.
[24]. Mikhaylichenko, S.; Dounin, V.; Zaplishny, V. Effectivity of the PASS program in Predicting Biological Activity for sym-Triazine Derivatives. *Fourth International Symposium on Computational*

Methods in Toxicology and Pharmacology Integrating Internet Resources, Moscow, Russia, September 1-5, **2007**.
[25]. Mikhaylichenko, S.; Dounin, V.; Zaplishny, V.; Chesnyuk, A. Synthesis and Potential Bioactivity of New Pyrazolyl-sym-Triazine Derivatives. *Fourth International Symposium on Computational Methods in Toxicology and Pharmacology Integrating Internet Resources*, Moscow, Russia, September 1-5, **2007**.
[26]. Chesnyuk, A.; Mikhaylichenko, S.; Konyushkin, L.; Kotlyarov, N.; Zaplishny, V. Patent RU, *Chem. Abstr.* **2005**, *144*, 22947.
[27]. Chesnyuk, A.; Mikhaylichenko, S.; Firgang, S.; Kotlyarov, N.; Zaplishny, V. Patent RU, *Chem. Abstr.* **2006**, *144*, 345097.
[28]. Chesnyuk, A.; Mikhaylichenko, S.; Konyushkin, L.; Kotlyarov, N.; Zaplishny, V. Patent RU, *Chem. Abstr.* **2005**, *144*, 345098.
[29]. Giacomelli, G.; Porcheddu , A.; Salaris, M. *Org. Lett.* **2003**, *5(15)*, 2715-2717.
[30]. Bethel, W. J.; Rowayton, R. Patent US 4, 939, 213, *Chem. Abstr.* **1990**.
[31]. Maffezzoni, R.; Zanda, M. *Tetrahedron Let.* **2008**, *49(35)*, 5129-5132.
[32]. Anandan, S. K.; Ward, J. S.; Brokx, R. D.; Denny, T.; Bray, M. R.; Patel, D. V.; Xiao, X. Y. *Bioorg. Med. Chem. Lett.* **2007**, *17(21)*, 5995-5999.
[33]. Hauser, C. R. Renfrow, W. B. *Org. Synth.* **1939**, *19*, 15-17.
[34]. Ho, C. Y.; Strobel, E.; Ralbovsky, J.; Galermo, R. A. *J. Org. Chem.* **2005**, *70(12)*, 4873-4875.
[35]. Jones, L. W. and Hurd, C. D. *J. Am. Chem. Soc.* **1921**, *43(11)*, 2422-2448.
[36]. Chesnyuk, A.; Mikhaylichenko, S.; Zavodnov, V.; Zaplishny, V. *Chem. Heterocycl. Compd.* **2002**, *38(2)*, 177-182.
[37]. Mikhaylichenko, S.; Chesnyuk, A.; Zavodnik, V.; Firgang, S.; Koniushkin L.; Zaplishny, V. *Chem. Heterocycl. Compd.* **2002**, *38(3)*, 292-299.
[38]. Gordon, A. J.; Ford, R. A. The Chemist's Companion. Handbook of Practical Data, Techniques, and References, John Wiley&Sons, 1973.
[39]. Jerry, R. M; Christina, N. H.; Paul, F. S. Techniques in Organic Chemistry, W. H. Freeman, 2006.
[40]. Mikhaylichenko, S.; Chesnyuk, A.; Konyushkin, L.; Zaplishny, V. *Russ. Chem. Bull.* **2003,** *52(10)*, 2157-2160.
[41]. Chesnyuk, A.; Mikhaylichenko, S.; Konyushkin, L.; Firgang, S.; Zaplishny, V. *Russ. Chem. Bull.* **2005,** *54(8)*, 1900-1906.
[42]. Mikhaylichenko, S.; Chesnyuk, A.; Konyushkin, L.; Zaplishny, V. *Chem. Heterocycl. Compd*. **2006,** *42(5)*, 642-647.
[43]. Chesnyuk, A.; Mikhaylichenko, S.; Zaplishny, V.; Konyushkin, L.; Firgang, S.; *Chem. Heterocycl. Compd*. **2008,** *44(3)*, 339-348.
[44]. Vogel, A. J.; Tatchell, A. R.; Furnis, B. S.; Hannaford, A. J.; Smith, P. W. G. Vogel's Textbook of Practical Organic Chemistry, 5th edition, Prentice Hall, 1996.