Chemistry of Heterocyclic Compounds, Vol. 44, No. 12, 2008

TRANSFORMATIONS OF TETRAHYDRO-PYRIDO[4,3-*d*]PYRIMIDINES [*b*]-CONDENSED WITH ISOXAZOLE, THIAZOLE, THIADIAZOLE, AND TRIAZOLE UNITS UNDER THE ACTION OF ACTIVATED ALKYNES

L. G. Voskressensky, T. N. Borisova, M. V. Ovcharov, L. N. Kulikova, E. A. Sorokina, R. S. Borisov, and A.V. Varlamov

It has been established that 5-vinyl-substituted (N-R,N-vinylaminomethyl)isoxazolo(thiazolo, thiadiazolo)pyrimidines are formed when tetrahydropyrido[3,4-d]pyrimidines, annelated with isoxazole, thiazole, and thiadiazole units are treated with terminal alkynes as a result of opening of the tetrahydropyridine ring. 7-Methoxymethyl-substituted [N-R,N-(dimethoxycarbonylvinyl)]aminoethyl-isoxazolo- and thiazolopyrimi-dines were obtained by reaction with dimethyl acetylenedicarboxylate (ADCE). Triazolo-pyrimidoazocine was obtained for the first time from tetrahydrotriazolopyrimidine and methyl propiolate.

Keywords: vinyl-substituted isoxazolopyrimidone, vinyl-substituted thiadiazolopyrimidone, vinyl-substituted thiazolopyrimidinone, triazolopyrimidoazocine, ring scission.

Tetrahydropyridines, [*c*]-condensed with π-excessive pyrrole, indole, and thiophene units or with a benzene ring are converted to either condensed azocines [1] or azonines [2] under the influence of activated alkynes in methanol or acetonitrile, or form products from the opening of the tetrahydropyridine with the participation of a methanol molecule – the corresponding methoxy-substituted heterocycles with α-vinyl-aminoethyl groups, which may cyclize under the influence of a Lewis acids into condensed azocines [3, 4].

Tetrahydropyrido[4,3-*d*]pyrimidines were converted into N-methyl- and N-benzyl-substituted pyrimido-[4,3-*d*]azocines under the influence of methyl and ethyl propiolate at 25°C by the elimination of the piperidine unit [5, 6].

Considering that polycyclic compounds with pyrimidine units are of interest in the plan to study cytotoxic activity, we have carried out the synthesis of tetrahydropyrido[4,3-*d*]pyrimidines [7] condensed with isoxazole, thiazole, thiadiazole, and triazole units, and we have studied their reactions with methyl propiolate, acetylacetylene, and dimethyl acetylenedicarboxylate (ADCE). In this way, apart from obtaining the original condensed azocines, we planned to study the effect of the type of condensed azole ring on the direction of the

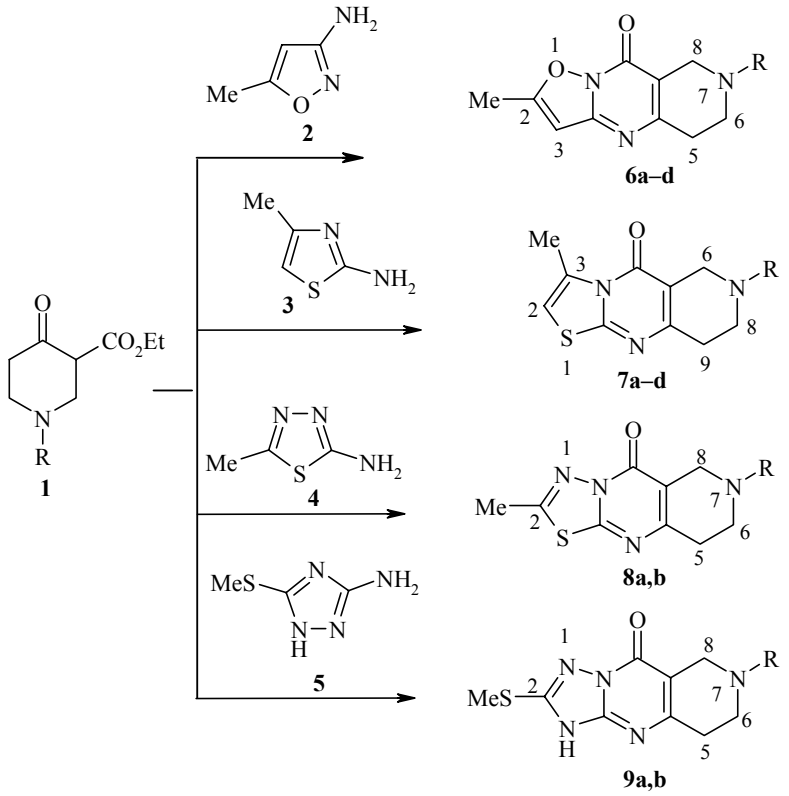
* Dedicated to Academician B. A. Trofimov on his 70th jubilee.

Peoples' Friendship University of Russia, Moscow 117198, Russia; e-mail: maxovcharov@rambler.ru.
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, 1861-1872, December, 2008. Original article submitted May 15, 2008.

 0009-3122/08/4412-1510

transformation of the tetrahydropyridine fragment. The condensed tetrahydropyrimidines **6-9** were obtained in 30–80% yields by the condensation of 3-ethoxycarbonylpiperidin-4-ones **1** with 3-amino-5-methylisoxazole (**2**), 2-amino-4-methylthiazole (**3**), 2-amino-5-methylthiadiazole (**4**), and 3-amino-5-methylthiotriazole-1,2,4 (**5**) in polyphosphoric acid at 80°C.

Scheme 1



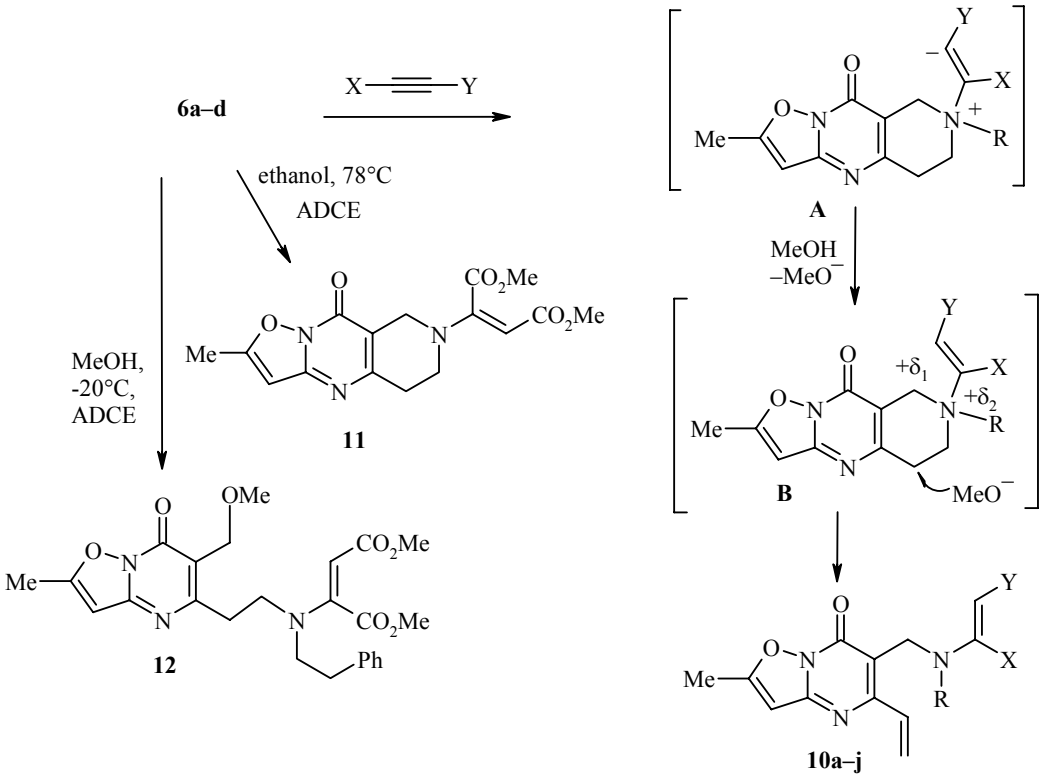
6–9 a R = Me; **6–8 b** R = Bn; **6c, 7c** R = *i*-Pr; **6d, 7d, 9b** R = CH_2CH_2Ph

Reactions of compounds **6-9** with ADCE, methyl propiolate, and acetylacetylene were carried out in methanol or ethanol at temperatures from -20 to 78°C. When isoxazolopyridopyrimidines reacted with alkynes in methanol at 20°C opening of the tetrahydropyridine ring occurred to give 5-vinyl-6-(N-vinyl-N-R-amino)-ethylisoxazolo[3,2-*b*]pyrimidines **10a-j** in yields of 50-85%.

The reactions begin with the addition of the nitrogen atom of the tetrahydropyridine fragment to the triple bond of the alkyne, as a result an ammonium zwitter-ion **A** is formed which removes a proton from a methanol molecule to form the cation **B.** Hofmann degradation of the intermediate **B** under the influence of the methoxide anion leads to the vinyl-substituted compounds **10a-j**. This route of the process is probably explained by neutralization by the isoxazolopyrimidine unit of the deficit of electron density on atom C-8, which arises by quaternization, so that nucleophilic attack on this atom becomes disadvantageous.

Reaction of compound **6b** with ADCE in boiling methanol is accompanied by N-debenzylation of the intermediate ammonium cation **B**. 7-Dimethoxycarbonylvinyl-substituted isoxazolopyridopyrimidine **11** was obtained in 40% yield. Compound **12** was obtained in 30% yield from the reaction of the N-phenethyl-substituted compound **6d** with ADCE – this is the product of opening of the tetrahydropyridine ring with participation of the methanol molecule.

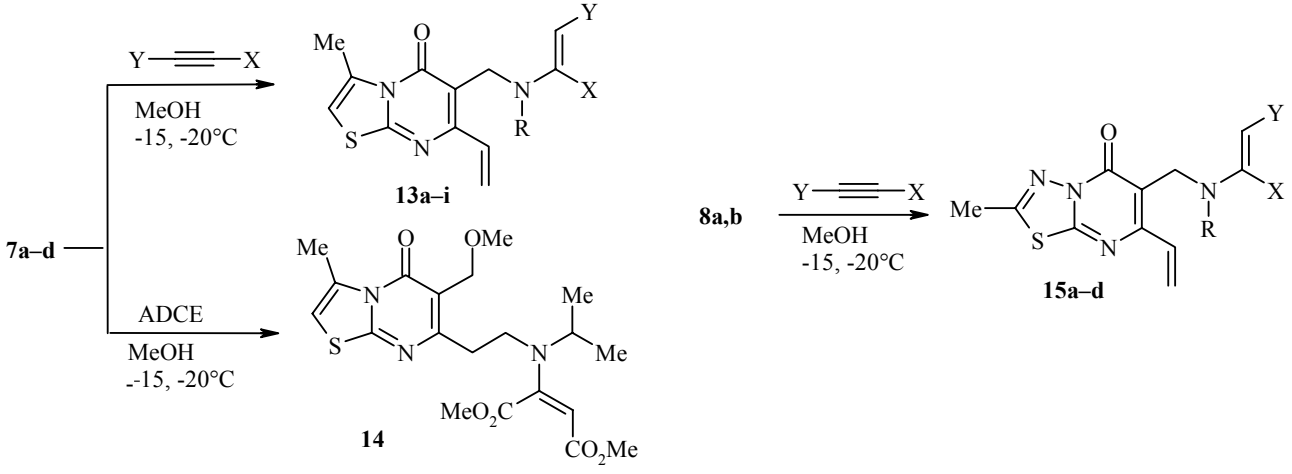
Scheme 2



10a–c R = Me; **d, e** R = Bn; **f–h** R = *i*-Pr; **i, j** R = CH_2CH_2Ph; **a, b, d–g, i, j** X = H; **c, h** X = CO_2Me; **a, c, d, f, h, i** Y = CO_2Me; **b, e, g, j** Y = COMe

Analogous opening of the tetrahydropyridine ring occurs on reaction of the thiazolo- and thiadiazolo-condensed pyridopyrimidines **7a-d** and **8a,b** with alkynes in methanol at temperatures from -15° to -20°. The 5-vinyl-substituted thiazolopyrimidines **13a-i** were obtained in 56-95% yields while the thiadiazolo-pyridopyrimidines **15a-d** were obtained in 20-60% yields (Scheme 3).

Scheme 3



13, **15 a** R = Me; **b–d** R = Bn; **13 e, f** R = *i*-Pr; **g–i** R = CH_2CH_2Ph; **13 a–c**, **e**, **f**, **g**, **h**, **15 a–c** X = H, **13 d**, **i**, **15d** X = CO_2Me; **13 a**, **b**, **d, e, g**, **i**, **15 a**, **b**, **d** Y = CO_2Me, **13c**, **f**, **h**, **15 c** Y = COMe

Table 1. Characteristics of the Compounds Synthesized

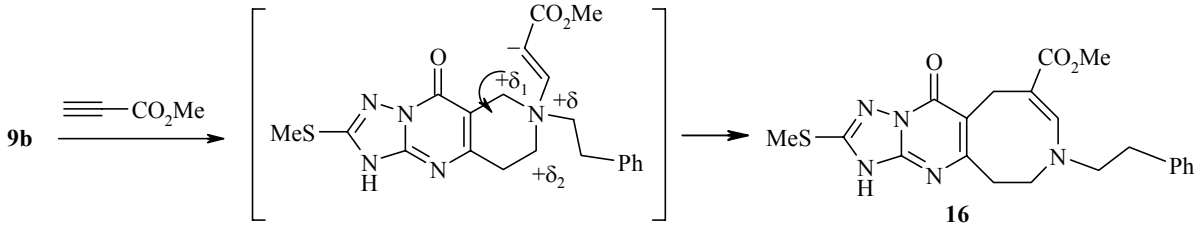
Compound	Empirical formula	Found, % / Calculated, %			mp, ºC	$[M+H]^+$	Yield, %
		C	H	N			
1	2	3	4	5	6	7	8
6a	$C_{11}H_{13}N_3O_2$	60.03 / 60.27	6.12 / 5.94	19.00 / 19.18	188-189	220	80
6b	$C_{17}H_{17}N_3O_2$	69.28 / 69.15	5.48 / 5.76	14.08 / 14.24	172-173	296	50
6c	$C_{13}H_{17}N_3O_2$	64.25 / 63.16	6.59 / 6.88	17.12 / 17.00	146-148	248	45
6d	$C_{18}H_{19}N_3O_2$	69.83 / 69.90	6.32 / 6.15	13.40 / 13.59	163-165	310	70
7a	$C_{11}H_{13}N_3OS$	56.29 / 56.17	5.34 / 5.53	17.95 / 17.87	138-140	236	40
7b	$C_{17}H_{17}N_3OS$	65.41 / 65.39	5.32 / 5.47	13.35 / 13.30	172-173	312	60
7c	$C_{13}H_{17}N_3OS$	59.45 / 59.32	6.29 / 6.46	16.10 / 15.97	146-148	264	33
7d	$C_{18}H_{19}N_3OS$	66.40 / 66.46	5.53 / 5.85	12.78 / 12.92	115-117	326	68
8a	$C_{10}H_{12}N_4OS$	50.97 / 50.85	4.91 / 5.08	23.84 / 23.73	160-162	237	37
8b	$C_{16}H_{16}N_4OS$	61.47 / 61.54	5.32 / 5.13	17.79 / 17.95	168-169	313	62
9a	$C_{10}H_{13}N_3OS$	47.69 / 47.81	4.97 / 5.18	27.95 / 27.89	185-187	252	30
9b	$C_{17}H_{19}N_5OS$	59.63 / 59.82	5.64 / 5.57	20.37 / 20.33	194-196	342	47
10a	$C_{15}H_{17}N_3O_4$	59.62 / 59.41	5.37 / 5.61	13.95 / 13.86	175-176	304	85
10b	$C_{15}H_{17}N_3O_3$	62.38 / 62.72	5.81 / 5.92	14.41 / 14.63	210-211	288	85
10c	$C_{17}H_{19}N_3O_6$	56.65 / 56.51	5.03 / 5.26	11.80 / 11.63	159-161	362	59
10d	$C_{21}H_{21}N_3O_4$	66.31 / 66.49	5.61 / 5.54	11.23 / 11.08	135-137	380	50
10e	$C_{21}H_{21}N_3O_3$	69.38 / 69.42	5.58 / 5.79	11.40 / 11.57	133-135	364	81
10f	$C_{17}H_{21}N_3O_4$	61.53 / 61.63	6.39 / 6.34	12.84 / 12.69	147-148	332	73
10g	$C_{17}H_{21}N_3O_3$	64.87 / 64.76	6.74 / 6.67	13.50 / 13.33	141-142	316	81
10h	$C_{19}H_{23}N_3O_6$	58.43 / 58.61	5.75 / 5.91	11.00 / 10.80	161-163	390	59
10i	$C_{22}H_{23}N_3O_4$	67.03 / 67.18	5.49 / 5.85	11.72 / 10.69	180-182	394	77
10j	$C_{22}H_{23}N_3O_3$	70.23 / 70.01	6.21 / 6.10	11.00 / 11.14	199-200	378	83
11	$C_{16}H_{17}N_3O_6$	53.21 / 53.33	5.05 / 4.90	12.23 / 12.10	210-212	348	30
12	$C_{25}H_{29}N_3O_7$	62.29 / 62.10	5.86 / 6.00	8.57 / 8.70	186-188	484	74
13a	$C_{15}H_{17}N_3O_3S$	56.58 / 56.43	5.26 / 5.33	13.03 / 13.17	144-145	320	78
13b	$C_{21}H_{21}N_3O_3S$	63.58 / 63.80	5.22 / 5.32	10.80 / 10.63	150-152	396	76
13c	$C_{21}H_{21}N_3O_2S$	66.31 / 66.49	5.73 / 5.54	11.19 / 11.08	125-126	380	65
13d	$C_{23}H_{23}N_3O_5S$	61.10 / 60.93	5.26 / 5.08	9.03 / 9.27	156-153	454	59
13e	$C_{17}H_{21}N_3O_3S$	58.53 / 58.79	6.21 / 6.05	11.97 / 12.10	138-140	348	75
13f	$C_{17}H_{21}N_3O_2S$	61.80 / 61.63	6.29 / 6.34	12.75 / 12.69	125-126	332	69

Table 1 (continued)

1	2	3	4	5	6	7	8
13g	$C_{22}H_{23}N_3O_3S$	64.59 / 64.55	5.80 / 5.62	10.30 / 10.26	155-156	410	85
13h	$C_{22}H_{23}N_3O_2S$	67.00 / 67.18	5.68 / 5.85	10.51 / 10.69	121-123	394	95
13i	$C_{24}H_{25}N_3O_5S$	61.53 / 61.67	5.43 / 5.35	9.10 / 8.99	150-152	468	76
14	$C_{20}H_{27}N_3O_6S$	53.78 / 54.92	6.31 / 6.18	9.92 / 9.61	140-142	438	56
15a	$C_{14}H_{16}N_4O_3S$	52.63 / 52.50	5.13 / 5.00	17.38 / 17.50	131-133	321	60
15b	$C_{20}H_{20}N_4O_3S$	60.38 / 60.61	4.95 / 5.05	14.30 / 14.14	138-140	397	48
15c	$C_{20}H_{20}N_4O_2S$	63.35 / 63.16	5.00 / 5.26	14.91 / 14.74	134-136	381	52
15d	$C_{22}H_{22}N_4O_5S$	58.02 / 58.14	4.93 / 4.85	12.19 / 12.33	124-126	455	20
16	$C_{21}H_{23}N_5O_3S$	59.42 / 59.29	5.28 / 5.41	16.53 / 16.47	249-250	426	52

Because of the poor solubility of triazolopyridopyrimidine **9b** its reaction with methyl propiolate was carried out in boiling methanol. A white precipitate of the azocine **16** appeared 15 min after addition of the alkyne – the product of the tandem enlargement of the tetrahydropyridine unit of the molecule.

Scheme 4



Apparently the triazolopyrimidine fragment, unlike the isoxazolo-, thiazolo-, and thiadiazolopyrimidine fragments, can stabilize the S_N2 transition state conducting to widening the tetrahydropyridine ring.

The structures of compounds **10-16** were confirmed with a complex of spectral data. In the mass spectra of all the compounds $[M+1]^+$ ion peaks were observed corresponding to the molecular formulas. The ^{1}H NMR spectra of vinyl-substituted compounds **10**, **13**, and **15** were characterized by the presence of three groups of signals of the protons of the vinyl groups at 5.68-5.78, 6.44-6.55, and 6.67-7.03 ppm, as doublets of doublets with characteristic vinyl (^3J = 10.0-10.5 and 16.0-16.9) and geminal (^2J = 2.0 Hz) coupling constants. The protons of the enamine fragment of the molecules appeared either as doublets at 4.60-5.30 and 7.61-7.85 ppm with characteristic $^3J_{trans}$ =11.0-13.0 Hz, or singlets in 4.74-5.30 ppm range. The azonine **16** has an intense $[M+1]^+$ peak in the chromato mass spectrum. In the ^{1}H NMR spectrum there are four signals for CH_2 protons at 2.71, 3.25, 3.40, and 3.84 ppm appearing as triplets, and singlet signal of the 6-CH_2 protons at 3.78 ppm. The presence of a singlet signal of the C-8 proton of the enamine unit at 7.28 ppm unambiguously confirms to azocine structure of compound **16**.

Table 2. IR and ^{1}H NMR Spectra of the Compounds Synthesized

Com-pound	IR spectrum, ν, cm^{-1} (C=O)	^{1}H NMR spectrum, δ, ppm (*J*, Hz)*
1	2	3
6a	1661	2.56 (3H, s, 7-CH_3); 2.75 (3H, s, 2-CH_3); 2.77 (2H, t, *J* = 6.2, H-5); 2.84 (2H, t, *J* = 6.2, H-6); 3.66 (2H, s, H-8); 6.20 (1H, s, H-3)
6b	1666	2.51 (3H, s, 2-CH_3); 2.75 (2H, t, *J* = 6.4, H-5); 2.8 (2H, t, *J* = 6.4, H-6); 3.66 (2H, s, H-8); 4.45 (2H, s, C$\underline{H}_2C_6H_5$); 6.22 (1H, s, H-3); 7.11-7.40 (5H, m, H arom.)
6c	1680	1.12 (6H, d, *J* = 6.5, 2CH_3); 2.51 (3H, s, 2-CH_3); 2.78 (2H, t, *J* = 6.2, H-5); 2.83 (2H, s, *J* = 6.2, H-6); 2.96 (1H, sept, *J* = 6.5, C$\underline{H}(CH_3)_2$); 3.66 (2H, s, H-8); 6.2 (1H, s, H-3)
6d	1666	2.52 (3H, s, 2-CH_3); 2.65–2.75 (4H, m, H-5,6); 2.79 (2H, m, $CH_2CH_2C_6H_5$); 3.34 (2H, s, H-8); 3.43 (2H, m, C$\underline{H}_2CH_2C_6H_5$); 6.68 (1H, s, H-3); 7.15-7.35 (5H, m, H arom.)
7a	1668	2.50 (3H, s, 7-CH_3); 2.70 (2H, m, H-8); 2.80 (3H, s, 3-CH_3); 2.81 (2H, m, H-9), 3.47 (2H, s, H-6), 6.35 (1H, s, H-2)
7b	1655	2.71 (2H, t, H-8); 2.81 (3H, s, 3-CH_3); 2.83 (2H, m, H-9); 3.47 (2H, s, H-6); 4.39 (2H, s, $CH_2C_6H_5$); 6.35 (1H, s, H-2); 7.30-7.65 (5H, m, H arom.)
7c	1660	1.13 (6H, d, *J* = 6.7, 2CH_3,); 2.70 (2H, t, *J* = 6.2, H-8); 2.80 (3H, s, 3-CH_3); 2.81 (2H, m, H-9); 2.95 (1H, sept, *J* = 6.7, C$\underline{H}(CH_3)_2$); 3.54 (2H, s, H-6); 6.34 (1H, s, H-2)
7d	1661	2.73 (2H, t, *J* = 6.4, H-8); 2.85 (3H, s, 3-CH_3); 2.87 (2H, m, H-9); 3.47 (2H, s, H-6); 4.49 (2H, m, $CH_2C\underline{H}_2C_6H_5$); 4.39 (2H, m, C$\underline{H}_2CH_2C_6H_5$); 6.35 (1H, s, H-2); 7.30-7.65 (5H, m, H arom.)
8a	1678	2.50 (3H, s, 7-CH_3); 2.71 (2H, m, H-9); 2.72 (3H, s, 2-CH_3); 2.84 (2H, m, H-8); 3.53 (2H, s, H-6)
8b	1682	2.72 (3H, s, 2-CH_3); 2.74 (2H, m, H-9); 2.80 (2H, m, H-8); 3.63 (2H, s, H-6); 3.74 (2H, s, C$\underline{H}_2C_6H_5$); 7.24–7.39 (5H, m, H arom.)
9a	1695	2.51 (3H, s, 2-CH_3); 2.56 (3H, s, 7-CH_3); 2.75 (2H, t, *J* = 7.0, H-9); 3.47 (2H, t, *J* = 7.0, H-8); 3.77 (2H, s, H-6)
9b	1698	2.56 (3H, s, 2-CH_3); 2.75 (2H, t, *J* = 7.0, H-9); 3.26 (2H, m, $CH_2C\underline{H}_2C_6H_5$); 3.47 (2H, t, *J* = 7.0, H-8); 3.77 (2H, c, H-6); 3.85 (2H, m, C$\underline{H}_2CH_2C_6H_5$); 7.08-7.20 (5H, m, H arom.)
10a	1667	2.55 (3H, s, 2-CH_3); 2.73 (3H, s, NCH_3); 3.63 (3H, s, OCH_3); 4.45 (2H, s, CH_2N); 4.60 (1H, d, *J* = 12.1, CH=); 5.73 (1H, dd, *J* = 10.0, *J* = 2.0, CH_2=); 6.31 (1H, s, H-3); 6.52 (1H, dd, *J* = 16.8, *J* = 2.0, CH_2=); 6.84 (1H, dd, *J* = 16.8, *J* = 10.0, CH=); 7.64 (1H, d, *J* = 12.1, CH=)
10b	1663	2.15 (3H, s, CH_3CO); 2.55 (3H, s, 2-CH_3); 2.78 (3H, s, NCH_3); 4.45 (2H, s, CH_2N); 5.13 (1H, d, *J* = 12.1, CH=); 5.75 (1H, dd, *J* = 10.0, *J* = 2.0, CH_2=); 6.34 (1H, s, 3-H); 6.55 (1H, dd, *J* = 16.8, *J* = 2.0, CH_2=); 6.88 (1H, dd, *J* = 16.8, *J* = 10.0, CH=); 7.70 (1H, d, *J* = 12.1, CH=)
10c	1671	2.54 (3H, s, 2-CH_3); 2.65 (3H, s, NCH_3); 3.62 (3H, s, OCH_3); 3.92 (3H, s, OCH_3); 4.36 (2H, s, CH_2N); 4.74 (1H, s, CH=); 5.70 (1H, dd, *J* = 10.5, *J* = 2.0, CH_2=); 6.31 (1H, s, H-3); 6.48 (1H, dd, *J* = 16.4, *J* = 2.0, CH_2=); 6.85 (1H, dd, *J* = 16.4, *J* = 10.5, CH=)
10d	1668	2.56 (3H, s, 2-CH_3); 3.67 (3H, s, OCH_3); 4.35 (2H, s, CH_2N); 4.55 (2H, s, C$\underline{H}_2C_6H_5$); 4.86 (1H, d, *J* = 13.0, CH=); 5.68 (1H, dd, *J* = 10.5, *J* = 2.0, CH_2=); 6.31 (1H, s, H-3); 6.50 (1H, dd, *J* = 16.4, *J* = 2.0, CH_2=); 6.67 (1H, dd, *J* = 16.4, *J* = 10.5, CH=); 7.15-7.29 (5H, m, H arom.); 7.70 (1H, d, *J* = 13.0, CH=)
10e	1673	2.11 (3H, s, CH_3CO); 2.56 (3H, s, 2-CH_3); 4.36 (2H, s, CH_2N); 4.49 (2H, s, C$\underline{H}_2C_6H_5$); 5.27 (1H, d, *J* = 13.0, CH=); 5.69 (1H, dd, *J* = 10.5, *J* = 2.0, CH_2=); 6.27 (1H, s, H-3); 6.49 (1H, dd, *J* = 16.8, *J* = 2.0, CH_2=); 6.77 (1H, dd, *J* = 16.8, *J* = 10.5, CH=); 7.15-7.29 (5H, m, H arom.); 7.84 (1H, d, *J* = 13.0, CH=)

Table 2 (continued)

1	2	3
10f	1668	1.17 (6H, d, J = 6.6, 2CH_3); 2.56 (3H, s, 2-CH_3); 3.67 (3H, s, OCH_3); 4.14 (1H, sept, J = 6.6, $CH(CH_3)_2$); 4.35 (2H, s, CH_2N); 4.86 (1H, d, J = 13.0, CH=); 5.68 (1H, dd, J = 10.5, J = 2.0, CH_2=); 6.31 (1H, s, H-3); 6.50 (1H, dd, J = 16.4, J = 2.0, CH_2=); 6.67 (1H, dd, J = 16.4, J = 10.5, CH=); 7.62 (1H, d, J = 13.0, CH=)
10g	1666	1.16 (6H, d, J = 6.6, 2CH_3); 2.15 (3H, s, CH_3CO); 2.56 (3H, s, 2-CH_3); 4.14 (1H, sept, J = 6.6, C<u>H</u>$(CH_3)_2$); 4.35 (2H, s, CH_2–N); 4.86 (1H, d, J = 13.0, CH=); 5.68 (1H, dd, J = 10.5, J = 2.0, CH_2=); 6.31 (1H, s, H-3); 6.50 (1H, dd, J = 16.4, J = 2.0, CH_2=); 6.67 (1H, dd, J = 16.4, J = 10.5, CH=); 7.62 (1H, d, J = 13.0, CH=)
10h	1671	1.21 (6H, d, J = 6.6, 2CH_3); 2.55 (3H, s, 2-CH_3); 3.50 (1H, m, C<u>H</u>$(CH_3)_2$); 3.61 (3H, s, OCH_3); 3.90 (3H, s, OCH_3); 4.39 (2H, s, CH_2N); 4.88 (1H, s, CH=); 5.70 (1H, dd, J = 10.5, J = 2.0, CH_2=); 6.29 (1H, s, H-3); 6.45 (1H, dd, J = 16.4, J = 2.0, CH_2=); 7.03 (1H, dd, J = 16.4, J = 10.5, CH=)
10i	1669	2.56 (3H, s, 2-CH_3); 2.75 (2H, m, C<u>H</u>$_2CH_2C_6H_5$); 3.23 (2H, m, CH_2C<u>H</u>$_2C_6H_5$); 3.53 (3H, s, OCH_3); 4.46 (2H, s, CH_2N); 4.64 (1H, d, J = 13.0, CH=); 5.68 (1H, dd, J = 10.5, J = 2.0, CH_2=); 6.31 (1H, s, H-3); 6.50 (1H, dd, J = 16.4, J = 2.0, CH_2=); 6.67 (1H, dd, J = 16.4, J = 10.5, CH=); 7.15-7.29 (5H, m, H arom.); 7.80 (1H, d, J = 13.0, CH=)
10j	1685	2.11 (3H, s, CH_3CO); 2.56 (3H, s, 2-CH_3); 2.76 (2H, m, C<u>H</u>$_2CH_2C_6H_5$); 3.23 (2H, m, CH_2C<u>H</u>$_2C_6H_5$); 4.37 (2H, s, CH_2N); 5.28 (1H, d, J = 13.0, CH=); 5.69 (1H, dd, J = 10.5, J = 1.8, CH_2=); 6.27 (1H, s, H-3); 6.49 (1H, dd, J = 16.5, J = 1.8, CH_2=); 6.78 (1H, dd, J = 16.5, J = 10.5, CH=); 7.15-7.29 (5H, m, H arom.); 7.83 (1H, d, J = 13.0, CH=)
11	1698	2.56 (3H, s, 2-CH_3); 2.87 (2H, t, J = 5.7, H-5); 3.46 (2H, t, J = 5.7, H-6); 3.65 (3H, s, OCH_3); 3.97 (3H, s, OCH_3); 4.21 (2H, s, 8-CH_2); 4.96 (1H, s, CH=); 6.28 (1H, s, H-3)
12	1698	2.56 (3H, s, 2-CH_3); 2.87 (2H, m, CH_2C<u>H</u>$_2C_6H_5$); 2.99 (2H, m, NC<u>H</u>$_2CH_2$); 3.34 (2H, m, C<u>H</u>$_2CH_2C_6H_5$); 3.40 (3H, s, CH_2OC<u>H</u>$_3$); 3.45 (2H, m, NCH_2C<u>H</u>$_2$); 3.66 (3H, s, OCH_3); 3.95 (3H, s, OCH_3); 4.46 (2H, s, C<u>H</u>$_2OCH_3$); 4.86 (1H, s, CH=); 6.27 (1H, s, H-3); 7.15-7.29 (5H, m, H arom.)
13a	1678	2.75 (3H, s, 3-CH_3); 2.79 (3H, s, CH_3N); 3.66 (3H, s, OCH_3); 4.34 (2H, s, CH_2N); 4.60 (1H, d, J = 12.1, CH=); 5.74 (1H, dd, J = 10.1, J = 2.0, CH_2=); 6.41 (1H, s, H-2); 6.55 (1H, dd, J = 16.7, J = 2.0, CH_2=); 6.83 (1H, dd, J = 16.7, J = 10.1, CH=); 7.63 (1H, d, J = 12.1, CH=)
13b	1673	2.65 (3H, s, 3-CH_3); 3.66 (3H, s, OCH_3); 4.33 (2H, s, CH_2N); 4.52 (2H, s, $CH_2C_6H_5$); 4.85 (1H, d, J = 12.4, CH=); 5.70 (1H, dd, J = 10.1, J = 2.0, CH_2=); 6.45 (1H, s, H-2); 6.55 (1H, dd, J = 16.7, J = 2.0, CH_2=); 6.99 (1H, dd, J = 16.7, J = 10.1, CH=); 7.04-7.28 (5H, m, H arom.); 7.71 (1H, d, J = 12.4, CH=)
13c	1666	2.11 (3H, s, CH_3CO); 2.79 (3H, s, 3-CH_3); 4.33 (2H, s, CH_2N); 4.35 (2H, s, $CH_2C_6H_5$); 4.85 (1H, d, J = 12.3, CH=); 5.70 (1H, dd, J = 10.1, J = 2.0, CH_2=); 6.45 (1H, s, H-2); 6.55 (1H, dd, J = 16.7, J = 2.0, CH_2=); 6.67 (1H, dd, J = 16.7, J = 10.1, CH=); 7.04-7.28 (5H, m, H arom.); 7.63 (1H, d, J = 12.3, CH=)
13d	1669	2.69 (3H, s, 3-CH_3); 3.65 (3H, s, OCH_3); 3.93 (3H, s, OCH_3); 4.33 (2H, s, CH_2N); 4.40 (2H, s, $CH_2C_6H_5$); 4.86 (1H, s, CH=); 5.72 (1H, dd, J = 10.5, J = 2.0, CH_2=); 6.34 (1H, s, H-2); 6.50 (1H, dd, J = 16.4, J = 2.0, CH_2=); 6.85 (1H, dd, J = 16.4, J = 10.5, CH=); 7.09-7.21 (5H, m, H arom.)
13e	1677	1.20 (6H, d, J = 6.2, 2CH_3); 2.80 (3H, s, 3-CH_3); 3.44 (1H, sept, J = 6.2, C<u>H</u>$(CH_3)_2$); 3.66 (3H, s, OCH_3); 4.30 (2H, s, CH_2N); 4.85 (1H, d, J = 12.1, CH=); 5.70 (1H, dd, J = 10.1, J = 2.0, CH_2=); 6.41 (1H, s, H-2); 6.55 (1H, dd, J = 16.7, J = 2.0, CH_2=); 6.71 (1H, dd, J = 16.7, J = 10.1, CH=); 7.62 (1H, d, J = 12.1, CH=)
13f	1667	1.22 (6H, d, J = 6.6, 2CH_3); 2.11 (3H, s, CH_3CO); 2.79 (3H, s, 3-CH_3); 3.40 (1H, sept, J = 6.6, C<u>H</u>$(CH_3)_2$); 4.35 (2H, s, CH_2N); 4.85 (1H, d, J = 12.4, CH=); 5.70 (1H, dd, J = 10.1, J = 2.0, CH_2=); 6.45 (1H, s, H-2); 6.55 (1H, dd, J = 16.7, J = 2.0, CH_2=); 6.67 (1H, dd, J = 16.7, J = 10.1, CH=); 7.63 (1H, d, J = 12.4, CH=)

Table 2 (continued)

1	2	3
13g	1677	2.67 (3H, s, 3-CH_3); 2.75 (2H, m, $CH_2C\underline{H}_2C_6H_5$); 3.23 (2H, m, $C\underline{H}_2CH_2C_6H_5$); 3.53 (3H, s, OCH_3); 4.37 (2H, s, CH_2N); 4.63 (1H, d, *J* = 12.0, CH=); 5.72 (1H, dd, *J* = 10.0, *J* = 2.0, CH_2=); 6.44 (1H, dd, *J* = 15.5, *J* = 2.0, CH_2=); 6.99 (1H, dd, *J* = 15.5, *J* = 10.0, CH=); 7.02 (1H, s, H-2); 7.09-7.21 (5H, m, H arom.); 7.57 (1H, d, *J* = 12.0, CH=)
13h	1666	2.11 (3H, s, CH_3CO); 2.80 (3H, s, 3-CH_3); 2.92 (2H, m, $CH_2C\underline{H}_2C_6H_5$); 3.19 (2H, m, $CH_2CH_2C_6H_5$); 4.37 (2H, s, CH_2N); 4.63 (1H, d, *J* = 12.2, CH=); 5.72 (1H, dd, *J* = 10.0, *J* = 2.0, CH_2=); 6.44 (1H, dd, *J* = 16.5, *J* = 2.0, CH_2=); 6.45 (1H, s, H-2); 6.99 (1H, dd, *J* = 16.5, *J* = 10.0, CH=); 7.09-7.21 (5H, m, H arom.); 7.57 (1H, d, *J* = 12.2, CH=)
13i	1686	2.71 (3H, s, 3-CH_3); 2.79 (2H, m, $CH_2C\underline{H}_2C_6H_5$); 3.13 (2H, m, $C\underline{H}_2CH_2C_6H_5$); 3.54 (3H, s, OCH_3); 3.81 (3H, s, OCH_3); 4.36 (2H, s, CH_2N); 4.98 (1H, s, CH=); 5.74 (1H, dd, *J* = 10.5, *J* = 2.0, CH_2=); 6.45 (1H, dd, *J* = 16.5, *J* = 2.0, CH_2=); 6.83 (1H, dd, *J* = 16.5, *J* = 10.5, CH=); 7.07 (1H, s, H-2); 7.12-7.28 (5H, m, H arom.)
14	1680	1.22 (6H, d, *J* = 6.6, $2CH_3$); 2.80 (3H, s, 3-CH_3); 2.94 (2H, t, *J* = 5.3, NCH_2CH_2); 3.40 (2H, t, *J* = 5.3, $NC\underline{H}_2CH_2$); 3.44 (3H, s, $CH_2OC\underline{H}_3$); 3.58 (1H, m, $C\underline{H}(CH_3)_2$); 3.64 (3H, s, OCH_3); 3.95 (3H, s, OCH_3); 4.42 (2H, s, CH_2OCH_3); 4.89 (1H, s, CH=); 6.41 (1H, s, H-2)
15a	1695	2.55 (3H, s, CH_3N); 2.75 (3H, s, 2-CH_3); 3.65 (3H, s, OCH_3); 4.41 (2H, s, CH_2N); 5.31 (1H, d, *J* = 12.4, CH=); 5.75 (1H, dd, *J* = 10.0, *J* = 2.0, CH_2=); 6.55 (1H, dd, *J* = 16.5, *J* = 2.0, CH_2=); 6.80 (1H, dd, *J* = 16.5, *J* = 10.5, CH=); 7.75 (1H, d, *J* = 12.4, CH=)
15b	1680	2.70 (3H, s, 2-CH_3); 3.65 (3H, s, OCH_3); 4.35 (2H, s, CH_2N); 4.45 (2H, s, $C\underline{H}_2C_6H_5$); 4.75 (1H, d, *J* = 13.0, CH=); 5.75 (1H, dd, *J* = 10.0, *J* = 2.0, CH_2=); 6.55 (1H, dd, *J* = 16.0, *J* = 2.0, CH_2=); 6.80 (1H, dd, *J* = 16.0, *J* = 10.0, CH=); 7.11-7.30 (5H, m, H arom.); 7.75 (1H, d, *J* = 13.0, CH=)
15c	1677	2.15 (3H, s, CH_3CO); 2.75 (3H, s, 2-CH_3); 4.40 (2H, s, CH_2–N); 4.55 (2H, s, $C\underline{H}_2C_6H_5$); 5.30 (1H, d, *J* = 13.0, CH=); 5.75 (1H, dd, *J* = 10.5, *J* = 2.0, CH_2=); 6.55 (1H, dd, *J* = 16.5, *J* = 2.0, CH_2=); 6.80 (1H, dd, *J* = 16.5, *J* = 10.5, CH=); 7.15-7.30 (5H, m, H arom.); 7.75 (1H, d, *J* = 13.0, CH=)
15d	1698	2.75 (3H, s, 2-CH_3); 3.65 (3H, s, OCH_3); 3.97 (3H, s, OCH_3); 4.40 (2H, s, CH_2N); 4.55 (2H, s, $C\underline{H}_2C_6H_5$); 5.30 (1H, s, CH=); 5.75 (1H, dd, *J* = 10.5, *J* = 2.0, CH_2=); 6.55 (1H, dd, *J* = 16.5, *J* = 2.0, CH_2=); 6.80 (1H, dd, *J* = 16.5, *J* = 10.5, CH=); 7.15-7.30 (5H, m, H arom.)
16	1681	2.56 (3H, s, SCH_3); 2.71 (2H, t, *J* = 7.4, $CH_2C\underline{H}_2C_6H_5$); 3.25 (2H, t, *J* = 6.5, H-11); 3.40 (2H, t, *J* = 7.4, $C\underline{H}_2CH_2C_6H_5$); 3.51 (3H, s, OCH_3); 3.78 (2H, s, H-6); 3.84 (2H, t, *J* = 6.5, H-10); 7.07-7.17 (5H, m, H arom.); 7.28 (1H, s, H-8)

* ^{1}H NMR spectra were recorded in $CDCl_3$ (compounds **6a-d**, **7a-d**, **8a,b**, **9a,b**, **10a-h**,**j**, **11, 13a-f**,**h, 14**, **15a-d**) and in DMSO-d_6 (compounds **10i**, **12, 13g,**i, **16**).

EXPERIMENTAL

IR spectra of the compounds synthesized were recorded in KBr disks with an INFRALYuM FT 801 Fourier spectrometer. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker WH-400 spectrometer (400 and 100 MHz respectively) with TMS as internal standard). Chromato-mass spectra were obtained with an Adilent 1100 series mass spectrometer LCSMD Trap System VL under EI ionization. TLC was carried out on Silufol plates in the chloroform–methanol 9:1 system (development with iodine vapor or a $KMnO_4$ solution (3g/l) in 0.008 mol/l H_2SO_4 solution).

Table 3. ^{13}C NMR Spectra of the Compounds Synthesized

Com-pound	Chemical shifts, δ, ppm*
6c	12.6, 18.5 (2C), 32.8, 44.9, 45.2, 53.6, 99.3, 112.6, 131.8, 152.0, 159.7, 166.9
6d	12.6, 32.1, 33.7, 49.5, 49.6, 59.4, 99.3, 112.0, 126.2, 128.6 (2C), 129.1 (2C), 140.7, 151.9, 152.0, 159.6, 168.8
7d	18.3, 31.6, 33.4, 49.5, 59.5, 106.8, 112.0, 126.2, 128.6 (2C), 129.1 (2C), 135.4, 140.7, 158.0, 159.8, 161.8
10i	12.7, 39.1, 40.7 (2C), 50.3, 83.8, 100.0, 111.2, 124.7, 126.6, 128.8 (2C), 129.0 (2C), 132.0, 139.0, 152.1, 153.1, 154.1, 157.6, 168.4, 169.1
12	12.7, 39.1, 40.7 (2C), 50.7, 53.0, 57.8, 64.5, 83.6, 99.8, 113.3. 126.8, 128.9 (2C), 129.1 (2C), 138.6, 153.4, 154.1, 164.5, 165.6, 167.4, 168.4
13b	18.1, 18.2, 50.2, 50.3, 84.5 (2C), 107.6, 110.9, 124.9, 127.0, 128.6 (2C), 131.4 (2C), 35.7, 137.7, 153.0, 155.3, 162.0, 163.4, 169.1
13g	18.3, 40.2, 50.1, 50.2, 83.6, 107.8, 110.6, 125.0, 126.5, 128.7, 129.1 (2C), 131.5 (2C), 135.7, 139.1, 152.3, 155.2, 162.0, 163.5, 169.2
13i	18.3, 18.4, 43.1, 50.5, 50.8, 53.1, 85.5, 108.1, 109.4, 125.3, 126.7, 128.8 (2C), 128.9 (2C), 131.4, 135.8, 138.7, 154.5, 156.1, 162.2, 163.7, 165.7, 167.5
14	18.3, 20.7, 32.1, 40.2, 42.6, 50.6, 52.7, 53.0, 57.9, 64.7, 83.2, 107.8, 113.1, 135.9, 154.2, 161.3, 162.5, 164.0, 165.7, 167.5

^{13}C NMR spectra were recorded in $CDCl_3$ (compounds **6c** and **7d**) and DMSO-d_6 (compounds **6d**, **10i**, **12**, **13b,g,i** and **14**).

7-R-2-Methyl-5,6,7,8-tetrahydro-9H-isoxazolo[2,3-*a*]pyrido[4,3-*d*]pyrimidin-9-ones 6a-d, 7-R-3-Methyl-6,7,8,9-tetrahydro-5H-pyrido[4,3-*d*]thiazolo[3,2-*a*]-pyrimidin-5-ones 7a-d, 7-R-2-Methyl-6,7,8,9-tetrahydro-5H-pyrido[4,3-*d*]thiazolo[3,2-*a*]pyrimidin-5-ones 8a,b, 7-R-2-Methylthio-5,6,7,8-tetrahydro-3H-pyrido-[1,2,4]triazolo[1,5-*a*]pyrimidin-9-ones 9a,b (General Method). A solution of 1-alkyl-3-ethoxycarbonyl-piperidin-4-one hydrochloride (0.02 mol) and 3-amino-5-methylisoxazole, 2-amino-5-methylthiazole, 2-amino-5-methyl-1,3,4-thiadiazole, or 3-amino-5-methylthio-1,2,4-triazole (0.02 mol), respectively, in polyphosphoric acid (20 ml) were heated with stirring (4-40 h, TLC monitoring). The mixture was cooled, added to 100 ml water, and neutralized with 15% NaOH solution, and extracted with methylene chloride (5×75 ml). The extract was dried over magnesium sulfate. The residue, after distilling off the solvent, was recrystallized from ethyl acetate.

Methyl Esters of (*E*)-3-[N-R-(2-Methyl-7-oxo-5-vinyl-7H-isoxazolo[2,3-*a*]pyrimidin-6-yl)methyl-aminoacrylic Acids 10a,d,f,i, 2-Methyl-6-[N-R-(3-oxobuten-1-yl)aminomethyl]-5-vinyl-7H-isoxazolo[2,3-*a*]pyrimidin-6-ones 10b,e,g,j, Dimethyl 2-[N-R-(2-Methyl-7-oxo-5-vinyl-7H-isoxazolo[2,3-*a*]pyrimidin-6-yl)]-methylaminomaleates 10c,h (General Method). A solution of isoxazolopyridopyrimidine **6a-d** (0.9 mmol) in methanol (10 ml) was cooled to a temperature from -15 to -20°C, 1.1 mmol of the corresponding alkyne was added and the mixture was stirred at low temperature for 24-72 h (monitored by TLC). The methanol was removed in vacuum and the residue was crystallized from ether to give compounds **10a-g,j.**

Dimethyl 2-[2-Methyl-5,6,7,8-tetrahydro-5-oxo(isoxazolo[2,3-*a*]pyrido[4,3-*d*]pyrimidin-7-yl)]maleate (11). Acetylenedicarboxylic ester (1.2 mmol) was added to a solution of N-benzyl-substituted isoxazolopyridopyrimidine **6b** (0.9 mmol) in ethanol (10 ml) heated to 70°C. The mixture was boiled for 10 h (TLC monitoring). The precipitate which formed on cooling was filtered off to give the maleate **11**.

Methyl Esters of (*E*)-3-{N-R[(3-Methyl-5-oxo-7-vinyl-5H-thiazolo[3,2-*a*]pyrimidin-6-yl)methyl]}-aminoacrylic Acids 13a,b,e,g, (*E*)-6-{[-N-R-(3-Oxobut-1-enyl)amino]methyl}-3-methyl-7-viny-5H-thiazolo[3,2-*a*]pyrimidin-5-ones 13c,f,h, Dimethyl Esters of (*E*)-2-{N-R[(3-Methyl-5-oxo-7-vinyl-5H-thiazolo[3,2-*a*]pyrimidin-6-yl)methyl]}aminomaleates 13d,i, Dimethyl (*E*)-2-{3-Isopropyl[2-(3-methyl-

6-methoxymethyl-5-oxo-5H-thiazolo[3,2-*a*]pyrimidin-7-yl)ethyl]}aminomaleate (14), Methyl (*E*)-3-{N-R-[2-methyl-5-oxo-7-vinyl-5H-[1,3,4]thiadiazolo[3,2-*a*]pyrimidin-6-yl)methyl]}aminoacrylates 15a,b, (*E*)-6-{3-benzyl[(3-oxobut-1-enyl)amino]methyl}-2-methyl-7-vinyl-5H-[1,3,4]thiadiazolo[3,2-*a*]pyrimidin-5-one (15c), dimethyl (*E*)-2-{N-benzyl[(2-methyl-5-oxo-7-vinyl-3H-[1,3,4]thiadiazolo[3,2-*a*]pyrimidin-6-yl]methyl}amino-maleate (15d) (General Method). To a solution of thiazolopyridopyrimidine **7a-d** or thiazolopyrido-pyrimidinone **8a,b** (0.9 mmol) in methanol (10 ml) the corresponding alkyne (1.1 mmol) was added at a temperature from -15 to -20°C and maintained at the low temperature until the reaction was completed (TLC monitoring). The methanol was removed in vacuum. The residue was triturated with ether, filtered off and recrystallized from a mixture of hexane and ethyl acetate.

Methyl 2-methylthio-3,5,6,9,10,11-hexahydro-5-oxo-9-(2-phenethyl)-[1,2,4]triazolo[1',2':1,2]pyrimido-[4,5-*d*]azocin-7-carboxylate (16). A solution of triazolopyridopyrimidine **9b** (0.2 g, 0.6 mmol) and methyl propiolate (0.06 g, 0.74 mmol) in methanol (7 ml) was boiled for 30 min (TLC monitoring). The mixture was cooled, the precipitate was filtered off, washed with methanol and dried to give compound **16** (0.13 g).

This work was carried out with financial support from RFFI (grant 07-03-1209-ofi).

REFERENCES

1. A. V. Varlamov, T. N. Borisova, L. G. Voskressensky, T. A. Soklakova, L. N. Kulikova, A. I. Chernyshev, and G. G. Alexandrov, *Tetrahedron Lett.,* **43**, 6768 (2002).
2. L. G. Voskressensky, S. V. Akbulatov, T. N. Borisova, and A. V. Varlamov, *Tetrahedron,* **62,** 12392 (2006).
3. T. N. Borisova, L. G. Voskressensky, T. A. Soklakova, L. N. Kulikova, and A. V. Varlamov, *Molecular Diversity*, **6**, 202 (2003).
4. L. G. Voskressensky, T. N. Borisova, T. A. Soklakova, L. N. Kulikova, R. S. Borisov, and A. V. Varlamov, *Lett. Org. Chem.,* **2**, 18 (2005).
5. L. G. Voskressensky, T. N. Borisova, I. S. Kostenev, and L. N. Kulikova, *Tetrahedron Lett.,* **47**, 999 (2006).
6. L. G. Voskressensky, T. N. Borisova, I. S. Kostenev, I. V. Vorobiev, and A. V. Varlamov, *Tetrahedron Lett.,* **46**, 1975 (2005).
7. A. H. Cook and K. Y. Reed, *J. Chem. Soc.,* 399 (1945).