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SYNTHESIS OF PYRANO- AND THIOPYRANOPYRIDO-THIENOPYRIMIDINES AND PYRIMIDOTHIENOISO-QUINOLINES WITH A FUSED TRIAZOLE OR TETRAZOLE RING AT THE PYRIMIDINE RING

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Cyclocondensation reactions gave 7,10-dihydro-8H-pyrano- and 7,10-dihydro-8H-thiopyranopyrido-thienopyrimidines and 7,8,9,10-tetrahydropyrimidothienoisoquinolines with a fused triazole or tetrazole ring at the pyrimidine ring.

Keywords: 7,10-dihydro-8*H*-pyrano[4",3":4',5']pyrido[3',2':4,5]thieno[2,3-*e*]tetrazolo[1,5-*c*]pyrimidines, 7,10-dihydro-8*H*-pyrano[4",3":4',5']pyrido[3',2':4,5]thieno[2,3-*e*][1,2,4]triazolo[1,5-*c*(4,3-*c*)]pyrimidines, 7,8,9,10-tetrahydrotetrazolo[1",5":1',6']pyrimido[4',5':4,5]thieno[2,3-*c*]isoquinolines, 7,8,9,10-tetrahydro-[1,2,4]triazolo[1",5":1',6'(4",3":1',6')]pyrimido[4',5':4,5]thieno[2,3-*c*]isoquinolines, annelation, cyclo-condensation.

It is known that many condensed compounds with a thienopyrimidine fragment possess biological activity. Thus, amino-substituted derivatives of these compounds display antitumor [1], antimicrobial [2], and antiviral activity [3], while their piperazino-substituted analogs are antidepressants [4]; thienopyrimidinones display antihypertensive activity [5], while alkoxy-substituted derivatives may be used as fungicides [6].

The broad spectrum of biological activity of condensed thienopyrimidines and the possibility of further modification of their cyclic structure makes these compounds extremely attractive for the synthesis of new biologically active molecules.

The aim of the present work was to develop synthetic methods for 7,10-dihydro-8*H*-pyrano- and 7,10-dihydro-8*H*-thiopyranopyridothienopyrimidines and 7,8,9,10-tetrahydropyrimidothienoisoquinolines with a triazole or tetrazole ring fused at the pyrimidine ring.

These compounds were synthesized starting with previously described condensed derivatives of thieno[3,2-*d*]pyrimidine **1a-i** [7], which after conversion to the 8-chloro derivatives **2a-i** [8], were transformed to the corresponding 8-hydrazino derivatives **3a-i** [9-11]. Compounds **2b**, **3b**,**f** have been synthesized for the first time (Table 1).

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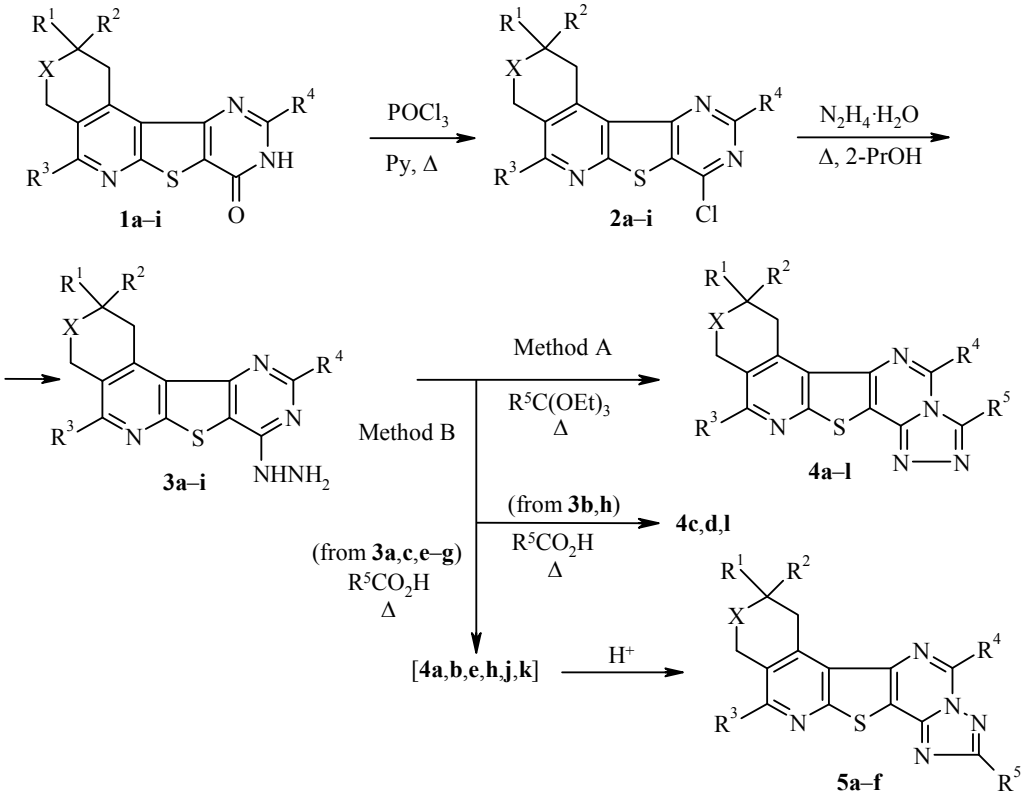
Heating hydrazino derivatives **3a-h** at reflux in accord with the procedure A leads to 1,2,4-triazolo[4,3-*c*]pyrimidines **4a-l**, while heating **3a-c**,**e-h** at reflux in accord with the procedure B leads to ambigouos results. Thus, hydrazines **3b**,**h** give triazolo[4,3-*c*]pyrimidines **4c**,**d**,**l** in high yield, while hydrazines **3a**,**c**,**e-g** give products **5a-f**, which are [1,5-*c*]-isomers of compounds **4a**,**b**,**e**,**h**,**j**,**k**. We should also note that maintaining the compound **3g** in formic acid (procedure C) leads only to the triazolopyrimidine **4k**.

These results suggest the initial formation of triazolopyrimidines **4**, which upon the action of acid may undergo Dimroth rearrangement with cleavage of the pyrimidine ring C–N bond, to give the isomers **5**. Triazolopyrimidines **4** display different stability relative to this rearrangement depending on the nature of pyrimidine ring substitution, as well as the reaction temperature.



1a–3a, **4a**,**b**, **5a**,**b** X = O, $R^1 = R^2$ = Me, R^3 = morpholin-4-yl, R^4 = H; **4a**, **5a** R^5 = H; **4b**, **5b** R^5 = Me;
1b–3b, **4c**,**d** X = O, $R^1 = R^2 = R^4$ = Me, R^3 = morpholin-4-yl; **4c** R^5 = H; **4d** R^5 = Me;
1c–3c, **4e**, **5c** X = O, $R^1 = R^2$ = Me, R^3 = morpholin-4-yl, R^4 = SBn; **4e**, **5c** R^5 = H;
1d–3d, **4f**,**g** X = O, $R^1 = R^2$ = Me, R^3 = pyrrolidin-1-yl, R^4 = H; **4f** R^5 = H; **4g** R^5 = Me;
1e–3e, **4h**,**i**, **5d** X = O, $R^1 = R^4$ = H, R^2 = *i*-Pr, R^3 = morpholin-4-yl; **4h**, **5d** R^5 = H; **4i** R^5 = Me;
1f–3f, **4j**, **5e** X = S, $R^1 = R^2$ = Me, R^3 = morpholin-4-yl, R^4 = H; **4j**, **5e** R^5 = H;
1g–3g, **4k**, **5f** X = CH_2, $R^1 = R^2 = R^4$ = H, R^3 = morpholin-4-yl, **4k**, **5f** R^5 = H;
1h–3h, **4l** X = CH_2, $R^1 = R^2$ = H, R^3 = morpholin-4-yl, R^4 = SMe; **4l** R^5 = H;
1i–3i X = CH_2, $R^1 = R^2$ = H, R^3 = morpholin-4-yl, R^4 = SBn

Thus, products **4c**,**d or 4l**, which contain a methyl or methylthio group at the C-4 atom of the pyrimidine ring, are stable upon heating at reflux in acid, while products **4a**,**b**,**h**,**j**,**k** or **4e**, which contain H or benzylthio groups, are readily converted to the corresponding isomers **5a-f**. Product **4k**, which is unstable upon heating at reflux, does not undergo rearrangement to isomer **5k** at 50-60°C.

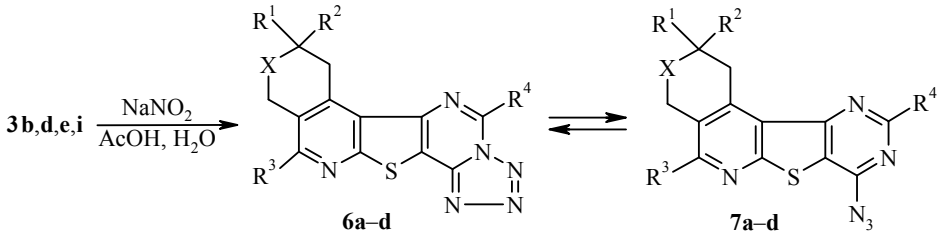
Isomers **4** and **5** with an unsubstituted triazole ring are readily distinguished by the position of the proton signal of this ring in the ^{1}H NMR spectra [12]: the H-3 proton signals in products **4** are found at

9.23-9.44 ppm, which is downfield from the H-2 signal in products **5** at 8.42-8.57 ppm. This finding is probably related to the magnetic anisotropy effect in the pyrimidine ring (Table 2). We also note that isomers **4** have higher melting points than the isomers **5** (Table 1).

Treatment of 8-hydrazinopyrimidines **3b**,**d**,**e**,**i** with aqueous sodium nitrite in acetic acid at room temperature leads to the formation of products, which may exist as a mixture of tetrazolo[1,5-*c*]thieno-[3,2-*d*]pyrimidines **6a-d** and their azide tautomers **7a-d**.

TABLE 1. Physicochemical Characteristics of Compounds **2-6**

Compound	Empirical formula	Found, % / Calculated, %				Mp, °C	Yield, % (method)	R_f
		C	H	N	S			
2b	$C_{19}H_{21}ClN_4O_2S$	56.22 / 56.36	5.32 / 5.23	13.62 / 13.84	7.72 / 7.92	253-255	75	0.61
3b	$C_{19}H_{24}N_6O_2S$	56.75 / 56.98	6.16 / 6.04	20.78 / 20.98	8.14 / 8.01	272-274	92	0.51
3f	$C_{18}H_{22}N_6OS_2$	53.65 / 53.71	5.36 / 5.51	20.71 / 20.88	15.81 / 15.93	272-274	94	0.53
4A	$C_{19}H_{20}N_6O_2S$	57.75 / 57.56	5.16 / 5.08	21.48 / 21.20	8.15 / 8.09	324-325	87 (A)	0.53
4b	$C_{20}H_{22}N_6O_2S$	58.41 / 58.52	5.48 / 5.40	20.63 / 20.47	7.65 / 7.81	334-336	70 (A)	0.48
4c	$C_{20}H_{22}N_6O_2S$	58.78 / 58.52	5.66 / 5.40	20.33 / 20.47	7.56 / 7.81	342-344	66 (A) 72 (B)	0.51
4d	$C_{21}H_{24}N_6O_2S$	59.68 / 59.41	5.76 / 5.70	19.61 / 19.80	7.49 / 7.55	305-307	75 (A) 68 (B)	0.48
4e	$C_{26}H_{26}N_6O_2S_2$	60.34 / 60.21	5.26 / 5.05	16.38 / 16.20	12.58 / 12.36	243-244	91 (A)	0.48
4f	$C_{19}H_{20}N_6OS$	59.78 / 59.98	5.56 / 5.30	22.18 / 22.09	8.56 / 8.43	307-309	92 (A)	0.52
4g	$C_{20}H_{22}N_6OS$	60.78 / 60.89	5.43 / 5.62	21.54 / 21.30	8.28 / 8.13	333-335	94 (A)	0.61
4h	$C_{20}H_{22}N_6O_2S$	58.32 / 58.52	5.46 / 5.40	20.63 / 20.47	7.56 / 7.81	300-302	88 (A)	0.62
4i	$C_{21}H_{24}N_6O_2S$	59.32 / 59.41	5.41 / 5.70	19.63 / 19.80	7.32 / 7.55	298-300	66 (A)	0.51
4j	$C_{19}H_{20}N_6OS_2$	55.42 / 55.32	4.67 / 4.89	20.52 / 20.37	15.62 / 15.55	318-320	94 (A)	0.55
4k	$C_{18}H_{18}N_6OS$	59.35 / 59.00	4.77 / 4.95	22.80 / 22.93	8.92 / 8.75	300-303	55 (A) 48 (C)	0.51
4l	$C_{19}H_{20}N_6OS_2$	55.45 / 55.32	4.77 / 4.89	20.50 / 20.37	15.31 / 15.55	300-301	81 (A) 64 (B)	0.48
5A	$C_{19}H_{20}N_6O_2S$	57.18 / 57.56	5.26 / 5.08	21.31 / 21.20	8.18 / 8.09	271-272	75 (B)	0.53
5b	$C_{20}H_{22}N_6O_2S$	58.41 / 58.52	5.52 / 5.40	20.31 / 20.47	7.76 / 7.81	248-250	72 (B)	0.53
5c	$C_{26}H_{26}N_6O_2S_2$	60.41 / 60.21	5.14 / 5.05	16.45 / 16.20	12.63 / 12.36	236-238	83 (B)	0.51
5d	$C_{20}H_{22}N_6O_2S$	58.32 / 58.52	5.45 / 5.40	20.61 / 20.47	7.64 / 7.81	243-245	61 (B)	0.48
5e	$C_{19}H_{20}N_6OS_2$	55.52 / 55.32	4.74 / 4.89	20.52 / 20.37	15.32 / 15.55	253-255	75 (B)	0.58
5f	$C_{18}H_{18}N_6OS$	59.23 / 59.00	4.78 / 4.95	22.74 / 22.93	8.56 / 8.75	219-221	71 (B)	0.53
6A	$C_{19}H_{21}N_7O_2S$	55.62 / 55.46	5.24 / 5.14	23.52 / 23.83	7.62 / 7.79	258-260	97	0.46
6b	$C_{18}H_{19}N_7OS$	56.78 / 56.68	5.16 / 5.02	25.58 / 25.70	8.22 / 8.41	214-216	76	0.62
6c	$C_{19}H_{21}N_7O_2S$	55.62 / 55.46	5.35 / 5.14	23.64 / 23.83	7.81 / 7.79	227-229	97	0.64
6d	$C_{24}H_{23}N_7OS_2$	58.74 / 58.87	4.56 / 4.73	20.16 / 20.03	13.26 / 13.10	231-233	98	0.44



6,**7 a** X = O, $R^1 = R^2 = R^4$ = Me, R^3 = morpholin-4-yl; **b** X = O, $R^1 = R^2$ = Me, R^3 = pyrrolidin-1-yl, R^4 = H; **c** X = O, $R^1 = R^4$ = H, R^2 = *i*-Pr, R^3 = morpholin-4-yl; **d** X = CH_2, $R^1 = R^2$ = H, R^3 = morpholin-4-yl, R^4 = SBn

The formation of such mixtures obtained from hydrazines **3d**,**e**,**i** was confirmed by the ^{1}H NMR spectra of products **6a-d**, in which a double signal is noted for some protons. The downfield signal of each pair was assigned to the protons of tetrazole tautomer **6a-d**, since they should be subjected to the effect of the aromatic tetrazole ring. The ratio of tautomers **6** and **7** was determined from the ratio of the peak intensities of the double signals: **6b:7b** = 55:45, **6c:7c** = 60:40, **6d:7d** = 83:17 (the fraction of **7a** is insignificant). The azide form **7** probably exists only in DMSO-d_6 solution during recording of the ^{1}H NMR spectrum and is not formed during the reaction. The IR spectra of the reaction products show signals at 1010-1100 cm^{-1} characteristic for the tetrazole ring, but lack bands at 2130-2150 cm^{-1} characteristic for the azide form. Similar azidotetrazole tautomerism is observed for tetrazolo[4,5-*a*]pyridines [13].

Thus, derivatives of new pentacyclic heterocyclic systems, namely, triazolo[4,3-*c*]pyrimdines, triazolo[1,5-*c*]pyrimidines and tetrazolo[1,5-*c*]pyrimidines, were synthesized in this study. The rearrangement of condensed triazolo[4,3-*c*]pyrimidines to triazolo[1,5-*c*]pyrimidines was carried out. Azidotetrazole tautomerism was established for condensed tetrazolo[1,5-*c*]pyrimidines.

EXPERIMENTAL

The IR spectra were recorded for vaseline mulls on a UR-20 spectrometer. The ^{1}H NMR spectra were recorded on a Mercury 300 spectrometer (300 MHz) in DMSO-d_6 with TMS as internal standard. The electron impact mass spectra were recorded on an MKh-1320 mass spectrometer with direct sample inlet into the ion source at 50 eV. The elemental analysis was carried out on a Euro EA 3000 Elemental Analyzer. The melting points were determined on a Boetius hot stage apparatus. The purity of the compounds was monitored by thin-layer chromatography on Silufol UV-254 plates with eluent systems: 2:1 ethanol–chloroform (for compound **2b**), 1:1 ethanol–chloroform (for compounds **3b**,**f**), 3:1:1 1-butanol–pyridine–ethanol (for compounds **4a-l**, **5a-f**), 1:1 chloroform–benzene (for compounds **6a-d**). Iodine vapor was used for visulization.

8-Chloro-2,2,10-trimethyl-5-(morpholin-4-yl)-1,4-dihydro-2*H*-pyrano[4'',3'':4',5']pyrido[3',2':4,5]-thieno[3,2-*d*]pyrimidine (2b). A mixture of compound **1b** (3.86 g, 0.01 mol), $POCl_3$ (40.0 ml), and pyridine (0.5 ml) was heated at reflux for 2 h. Excess $POCl_3$ was distilled off, the residue was cooled, diluted with ice water (100 ml), and neutralized with NH_3 aqueous solution. The crystals formed of compound **2b** were washed with water and recrystallized from 4:1 $CHCl_3$–EtOH,

8-Hydrazino-2,2,10-trimethyl-5-(morpholin-4-yl)-1,4-dihydro-2*H*-pyrano- (3b) and 8-Hydrazino-2,2-dimethyl-5-(morpholin-4-yl)-1,4-dihydro-2*H*-thiopyrano[4'',3'':4',5']pyrido[3',2':4,5]thieno[3,2-*d*]pyrimidine (3f) (General Method). Hydrazine hydrate (2 g, 0.04 mol) was added to compound **2b** or **2f** (0.01 ml) in absolute 2-propanol (40 ml), and the mixture was heated at reflux for 5 h. After cooling, the crystalline precipitate of compound **3b** or **3f** was filtered off, washed with water and ethanol, and recrystallized from 2:1 chloroform–ethanol.

Thienopyrimidine 3f. IR spectrum, ν, cm^{-1}: 1580-1600 (C=C_{Ar}), 3250-3300 ($NHNH_2$).

TABLE. ^{1}H NMR Spectra of Compounds **2-7**

Com-pound	Chemical shifts, δ, ppm (*J*, Hz)
1	2
2b	1.37 (6H, s, 2-$(CH_3)_2$); 2.80 (3H, s, 10-CH_3); 3.29-3.33 (4H, m, $N(CH_2)_2$); 3.46 (2H, s, 1-CH_2); 3.77-3.82 (4H, m, $O(CH_2)_2$); 4.68 (2H, s, 4-CH_2)
3b	1.34 (6H, s, 2-$(CH_3)_2$); 2.51 (3H, s, 10-CH_3); 3.15-3.19 (4H, m, $N(CH_2)_2$); 3.51 (2H, s, 1-CH_2); 3.76-3.80 (4H, m, $O(CH_2)_2$); 4.53 (2H, s, NH_2); 4.68 (2H, s, 4-CH_2); 8.48 (1H, s, NH)
3f	1.23 (6H, s, 2-$(CH_3)_2$); 3.19-3.25 (4H, m, $N(CH_2)_2$); 3.51 (2H, s, 1-CH_2); 3.79-3.84 (4H, m, $O(CH_2)_2$); 3.95 (2H, s, SCH_2); 4.51 (2H, s, NH_2); 8.29 (1H, s, NH); 8.41 (1H, s, H-10)
4a	1.38 (6H, s, 8-$(CH_3)_2$); 3.20-3.26 (4H, m, $N(CH_2)_2$); 3.51 (2H, s, 7-CH_2); 3.77-3.83 (4H, m, $O(CH_2)_2$); 4.72 (2H, s, 10-CH_2); 9.44 (1H, s, H-3(5)); 9.47 (1H, s, H-5(3))
4b	1.38 (6H, s, 8-$(CH_3)_2$); 2.81 (3H, s, 3-CH_3); 3.15-3.23 (4H, m, $N(CH_2)_2$); 3.41 (2H, s, 7-CH_2); 3.76-3.80 (4H, m, $O(CH_2)_2$); 4.66 (2H, s, 10-CH_2); 9.38 (1H, s, H-5)
4c	1.37 (6H, s, 8-$(CH_3)_2$); 3.01 (3H, s, 5-CH_3); 3.19-3.24 (4H, m, $N(CH_2)_2$); 3.50 (2H, s, 7-CH_2); 3.78-3.83 (4H, m, $O(CH_2)_2$); 4.71 (2H, s, 10-CH_2); 9.44 (1H, s, H-3)
4d	1.37 (6H, s, 8-$(CH_3)_2$); 3.02 (3H, s, 3-CH_3); 3.09 (3H, s, 5-CH_3); 3.17-3.23 (4H, m, $N(CH_2)_2$); 3.45 (2H, s, 7-CH_2); 3.78-3.82 (4H, m, $O(CH_2)_2$); 4.69 (2H, s, 10-CH_2)
4e	1.21 (6H, s, 8-$(CH_3)_2$); 3.21-3.25 (4H, m, $N(CH_2)_2$); 3.43 (2H, s, 7-CH_2); 3.78-3.83 (4H, m, $O(CH_2)_2$); 4.71 (2H, s, 10-CH_2); 4.82 (2H, s, SCH_2); 7.23-7.53 (5H, m, H Ph); 9.23 (1H, s, H-3)
4f	1.38 (6H, s, 8-$(CH_3)_2$); 1.94-2.05 (4H, m, $N(CH_2C\underline{H}_2)_2$); 3.44 (2H, s, 7-$CH_2$); 3.58-3.69 (4H, m, $N(CH_2)_2$); 4.80 (2H, s, 10-CH_2); 9.35 (1H, s, H-3(5)); 9.38 (1H, s, H-5(3))
4g	1.39 (6H, s, 8-$(CH_3)_2$); 1.95-2.05 (4H, m, $N(CH_2C\underline{H}_2)_2$); 2.82 (3H, s, 3-$CH_3$); 3.44 (2H, s, 7-$CH_2$); 3.59-3.69 (4H, m, $N(CH_2)_2$); 4.81 (2H, s, 10-CH_2); 9.18 (1H, s, H-5)
4h	1.09 (3H, d, ^3J = 6.7) and 1.11 (3H, d, ^3J = 6.7, $CH(C\underline{H}_3)_2$); 1.89 (1H, sept.d, ^3J = 6.7, ^3J = 6.3, $C\underline{H}(CH_3)_2$); 3.10-3.18 (2H, m) and 3.26-3.34 (2H, m, $N(CH_2)_2$); 3.18-3.23 (1H, m, 7-CH_A); 3.47 (1H, ddd, ^3J = 10.9, ^3J = 6.3, ^3J = 3.4, OCH); 3.69-3.78 (3H, m) and 3.81-3.89 (2H, m, $O(CH_2)_2$, 7-CH_B); 4.68 (1H, d, ^2J = 14.6) and 4.81 (1H, d, ^2J = 14.6, 10-CH_2); 9.43 (1H, s, H-3(5)); 9.44 (1H, s, H-5(3))
4i	1.09 (3H, d, ^3J = 6.7) and 1.10 (3H, d, ^3J = 6.7, $CH(C\underline{H}_3)_2$); 1.83-1.95 (1H, m, $C\underline{H}(CH_3)_2$); 2.88 (3H, s, 3-$C\underline{H}_3$); 3.10-3.34 (5H, m, $N(CH_2)_2$ and 7-CH_A); 3.44-3.52 (1H, m, OCH); 3.71-3.78 (3H, m) and 3.80-3.89 (2H, m, $O(CH_2)_2$, 7-CH_B); 4.68 (1H, d, ^2J = 14.7) and 4.82 (1H, d, ^2J = 14.7, 10-CH_2); 9.27 (1H, s, H-5)
4j	1.41 (6H, s, 8-$(CH_3)_2$); 3.24-3.29 (4H, m, $N(CH_2)_2$); 3.80-3.86 (8H, m, $O(CH_2)_2$, 7-CH_2 and SCH_2); 9.46 (1H, s, H-3(5)); 9.48 (1H, s, H-5(3))
4k	1.77-1.86 (2H, m) and 1.93-2.02 (2H, m, 8,9-CH_2); 2.76 (2H, t, ^3J = 5.8, 10-CH_2); 3.22-3.27 (4H, m, $N(CH_2)_2$); 3.62 (2H, t, ^3J = 6.5, 7-CH_2); 3.78-3.83 (4H, m, $O(CH_2)_2$); 9.39 (1H, s, H-3(5)); 9.41 (1H, s, H-5(3))
4l	1.74-1.84 (2H, m) and 1.91-2.00 (2H, m, 8,9-CH_2); 2.71-2.79 (2H, m) and 3.55-3.62 (2H, m, 7,10-CH_2); 2.88 (3H, s, SCH_3); 3.22-3.27 (4H, m, $N(CH_2)_2$); 3.77-3.83 (4H, m, $O(CH_2)_2$); 9.30 (1H, s, H-3)
5a	1.47 (6H, s, 8-$(CH_3)_2$); 3.23-3.29 (4H, m, $N(CH_2)_2$); 3.63 (2H, s, 7-CH_2); 3.78-3.84 (4H, m, $O(CH_2)_2$); 4.87 (2H, s, 10-CH_2); 8.57 (1H, s, H-2); 9.45 (1H, s, H-5)
5b	1.39 (6H, s, 8-$(CH_3)_2$); 2.78 (3H, s, 2-CH_3); 3.17-3.27 (4H, m, $N(CH_2)_2$); 3.46 (2H, s, 7-CH_2); 3.75-3.85 (4H, m, $O(CH_2)_2$); 4.68 (2H, s, 10-CH_2); 9.39 (1H, s, H-5)
5c	1.23 (6H, s, 8-$(CH_3)_2$); 3.20-3.25 (4H, m, $N(CH_2)_2$); 3.43 (2H, s, 7-CH_2); 3.77-3.82 (4H, m, $O(CH_2)_2$); 4.71 (2H, s, 10-CH_2); 4.82 (2H, s, SCH_2); 7.23-7.45 (5H, m, H Ph); 8.45 (1H, s, H-2)
5d	1.10 (3H, d, ^3J = 6.7) and 1.12 (3H, d, ^3J = 6.7, $CH(C\underline{H}_3)_2$); 1.90 (1H, sept.d, ^3J = 6.7, ^3J = 6.3, $C\underline{H}(CH_3)_2$); 3.12-3.36 (5H, m, $N(CH_2)_2$ and 7-CH_A); 3.48 (1H, ddd, ^3J = 11.0, ^3J = 6.3, ^3J = 3.6, OCH); 3.71-3.89 (5H, m, $O(CH_2)_2$ and 7-CH_B); 4.68 (1H, d, ^2J = 14.6) and 4.80 (1H, d, ^2J = 14.6, 10-CH_2); 8.47 (1H, s, H-2); 9.53 (1H, s, H-5)
5e	1.43 (6H, s, 8-$(CH_3)_2$); 3.26-3.31 (4H, m, $N(CH_2)_2$); 3.81-3.86 (8H, m, $O(CH_2)_2$, 7-CH_2, and SCH_2); 8.48 (1H, s, H-2); 9.58 (1H, s, H-5)

TABLE 2 (continued)

1	2
5f	1.78-1.86 (2H, m) and 1.95-2.04 (2H, m, 8,9-CH_2) 2.77 (2H, t, ^3J = 5.8, 10-CH_2); 3.25-3.30 (4H, m, $N(CH_2)_2$); 3.65 (2H, t, ^3J = 6.5, 7-CH_2); 3.78-3.83 (4H, m, $O(CH_2)_2$); 8.46 (1H, s, H-2); 9.55 (1H, s, H-5)
6a	1.40 (6H, s, 8-$(CH_3)_2$); 3.23 (3H, s, 5-CH_3); 3.26-3.31 (4H, m, $N(CH_2)_2$); 3.53 (2H, s, 7-CH_2); 3.79-3.83 (4H, m, $O(CH_2)_2$); 4.71 (2H, s, 10-CH_2)
6b, **7b**	1.37 (2.7H, s) and 1.40 (3.3H, s, 8-$(CH_3)_2$); 1.95-2.05 (4H, m, $N(CH_2C\underline{H}_2)_2$); 3.42 (0.9H, s) and 3.47 (1.1H, s, 7-CH_2); 3.63-3.72 (4H, m, $N(CH_2)_2$); 4.83 (0.9H, s) and 4.85 (1.1H, s, 10-CH_2); 8.77 (0.45H, s) and 9.95 (0.55H, s, H-5)
6s, 7c	1.07-1.14 (6H, m, $CH(C\underline{H}_3)_2$); 1.82-1.97 (1H, m, $C\underline{H}(CH_3)_2$); 3.11-3.41 (5H, m) and 3.42-3.53 (1H, m, 7-CH_2, $N(CH_2)_2$); 3.66-3.90 (5H, m, H-8, $O(CH_2)_2$); 4.64-4.79 (2H, m, 10-CH_2); 8.86 (0.4H, s) and 10.10 (0.6H, s, H-5)
6d, **7d**	1.71-1.82 (2H, m, 8-CH_2); 1.84-1.96 (2H, m, 9-CH_2); 2.69 (1.65H, t, ^3J = 5.7) and 2.74 (0.35H, t, ^3J = 5.7, 10-CH_2); 3.26-3.32 (4H, m, $N(CH_2)_2$); 3.47 (1.65H, t, ^3J = 6.5) and 3.52 (0.35H, t, ^3J = 6.5, 7-CH_2); 3.75-3.82 (4H, m, $O(CH_2)_2$); 4.48 (1.65H, s) and 4.81 (0.35H, s, SCH_2); 7.17-7.54 (5H, m, H Ph)

7,10-Dihydro-8*H*-pyrano- and 7,10-Dihydro-8*H*-thiopyrano[4",3":4',5']pyrido[3',2':4,5]thieno-[2,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidines 4a-j and 7,8,9,10-Tetrahydro[1,2,4]triazolo[4",3":1',6']pyrimido-[4',5':4,5]thieno[2,3-*c*]isoquinolines 4k,j (General Method).

A. A mixture of hydrazine **3a-h** (0.01 mol) and triethyl orthoformate or triethyl orthoacetate (0.70 mol) was heated at reflux for 15 h. The crystalline precipitate of product **4a-l** obtained upon cooling was filtered off, washed with water, and recrystallized from 2:1 chloroform–ethanol.

B. Products **4c**,**d**,**l** were synthesized similarly using compounds **3b**,**h** (the description is given below for the products **5**) and were identical in their R_f and mp values to samples obtained according to procedure A.

C. A mixture of compounds **3g** (3.56 g, 0.01 mol) and formic acid (10 ml) was maintained at 50-60°C for 2 h. The cooled mixture was neutralized by adding 1 N aqueous potassium hydroxide. The crystalline precipitate of compound **4k** was filtered off, washed with water, and recrystallized from 2:1 chloroform–ethanol. Product **4k** was identical in its R_f and mp values to a sample prepared according to procedure A.

Compound 4a. Mass spectrum, *m*/*z* (I_{rel}, %): 396 $[M]^+$ (100), 372 (78), 356 (28), 326 (25), 302 (62).

Compound 4b. Mass spectrum, *m*/*z* (I_{rel}, %): 410 $[M]^+$ (100), 351 (51), 294 (46), 241 (20), 187 (63), 130 (12).

Compound 4f. Mass spectrum, *m*/*z* (I_{rel}, %): 380 $[M]^+$ (100), 365 (17), 351 (15), 325 (16), 310 (72), 296 (15).

Compound 4g. IR spectrum (neat), ν, cm^{-1}: 1580 ($C{=}C_{arom}$), 1600 (C=N). Mass spectrum, *m*/*z* (I_{rel}, %): 412 $[M]^+$ (100), 383 (7), 381 (36), 355 (52), 354 (27), 327 (21).

Compound 4j. Mass spectrum, *m*/*z* (I_{rel}, %): 412 $[M]^+$ (100), 381 (46), 379 (61), 355 (52), 353 (68), 321 (47).

7,10-Dihydro-8*H*-pyrano- and 7,10-Dihydro-8*H*-thiopyrano[4",3":4',5']pyrido[3',2':4,5]thieno-[2,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidines 5a-e and 11-(Morpholin-4-yl)-7,8,9,10-tetrahydro[1,2,4]triazolo-[1",5":1',6']pyrimido[4',5':4,5]thieno[2,3-*c*]isoquinoline (5f) (General Method). A mixture of compounds **3a**,**c**,**e-g** (0.01 mol) and formic acid (68 ml, 1.80 mol) or acetic acid (69 ml, 1.20 mol) was heated for 5 h at reflux in a flask equipped with a condenser. The excess acid was then distilled off and the residue was neutralized by adding aqueous potassium hydroxide. The crystalline product **5a-f** was filtered off, washed with water, and recrystallized from 2:1 chloroform–ethanol.

7,10-Dihydro-8*H*-pyrano[4",3":4',5']pyrido[3',2':4,5]thieno[2,3-*e*]tetrazolo[1,5-*c*]pyrimidines 6a-c and 5-Benzylsulfanyl-11-(morpholin-4-yl)-7,8,9,10-tetrahydrotetrazolo[1",5":1',6']pyrimido[4',5':4,5]-thieno[2,3-*c*]isoquinoline (6d) (General Method). A solution of sodium nitrite (5 g, 0.072 mol) in water (25 ml) was added in portions to a suspension of compounds **3b**,**d**,**e**,**i** (0.010 mol) in acetic acid (69 ml,

1.200 mol). The reaction mixture was maintained at room temperature for 48 h with occasional stirring. The crystalline precipitate was filtered off, washed with water, and recrystallized from DMSO.

Products 6a-d. IR spectrum, ν, cm^{-1}: 1010-1100 (tetrazole), 1580-1600 ($C=C_{Ar}$), 1620-1630 (C=N).

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