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SYNTHESIS OF NEW SUBSTITUTED PYRAZOLO[1,5-a]-PYRIMIDINES AND PYRAZOLO[1,5-a]1,3,5-TRIAZINES

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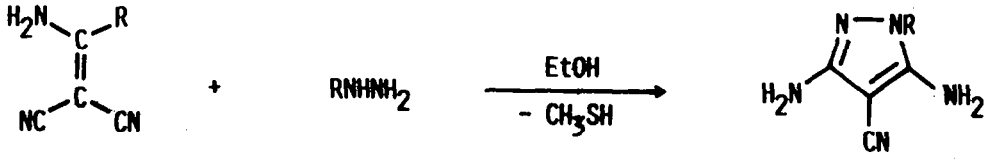
5-Substituted 3-amino-1H-pyrazole-4-carbonitriles **2a-d** react with appropriate biselectrophilic reagents in the presence of (TEA) to give the substitution products pyrazolo[1,5-a]pyrimidines **4a-d**, **6a-d** and pyrazolo[1,5-a]1,3,5-triazines **8a-d**. Compounds **6a** and **8a** react with secondary amines to **10a-c** and **11a-c**. Treatment of **2a** with malonodinitrile results in the substituted pyrazolo-[1,5-a]pyrimidine **16**. Condensation of **2a**, **2c** and **2d** with ethylidene-malodinitriles leads to racemic dihydro-pyrazolo[1,5-a]pyrimidines **18a-e**. Reaction of diene **20** with the heterodienophile **21** leads to formation of Diels-Alder adduct **22**.

Derivatives of the ring system pyrazolo[1,5-a]pyrimidine and pyrazolo[1,5-a]1,3,5-triazine show pharmacological activity according to the literature.

Amino-pyrazolo[1,5-a]pyrimidines are known as anti-cancer agents.[2,3] Various pyrazolo[1,5-a]pyrimidine derivates were synthesized as possible hypotensive and anxiolytic agents.[4] Pyrazolotriazinediones are applied as herbicides.[5]

Due the great interest for this class of pharmacologically active compounds, we have synthesized novel substituted pyrazolopyrimidines and pyrazolotriazines.

3,5-Diamino-1H-pyrazole-4-carbonitrile **2a** has been produced by treatment of enol ether **1a** with hydrazine.[6] In our synthesis we replaced enol ether **1a** by thioenol ether **1b** as ethylene reagent. Methyl hydrazine reacts with **1b** to give 3,5-diamino-1-methyl-1H-pyrazole-4-carbonitrile **2a**.



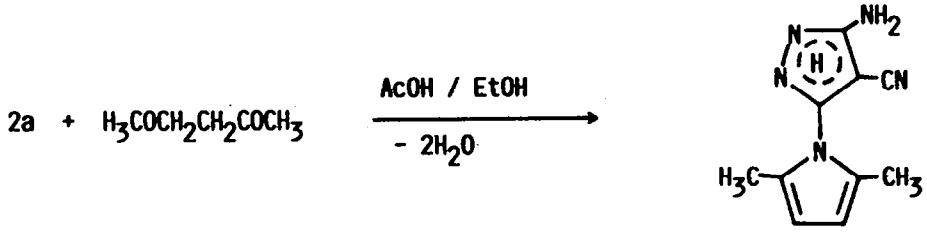
1a : R = $-O-(CH_2)_2OH$

1b : R = $-SCH_3$

2a : R = H

2e : R = CH_3

Aminopyrazole 2a was treated with acetonylacetone in the presence of acetic acid to give 2b by elimination of water.

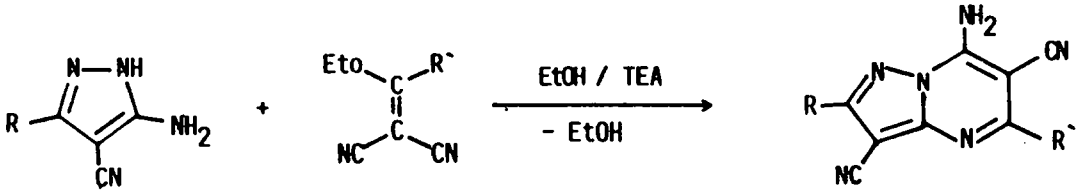


2b

Preparation of substituted 3-aminopyrazoles[5,7] 2c and 2d has been described in literature.

The substituted 3-aminopyrazoles 2a-d react with appropriate biselectrophilic reagents by being heated under reflux in basic conditions. Hereby alcohol or methylmercaptane is released, after which cyclization to the corresponding heterocyclic derivatives via attack of the cis-orientated nitrilo-C-atom takes place.

Reaction of 3-aminopyrazole with ethyl N-cyanoformimidate leads to formation of 4-amino-pyrazolo[1,5-a]1,3,5 triazine. Tam et al.[8] showed that this reaction did not produce the constitution isomer 2-amino-pyrazolotriazine. Compounds 4a-d can be produced likewise by reaction of 2a and 2b with 3a and 3b.

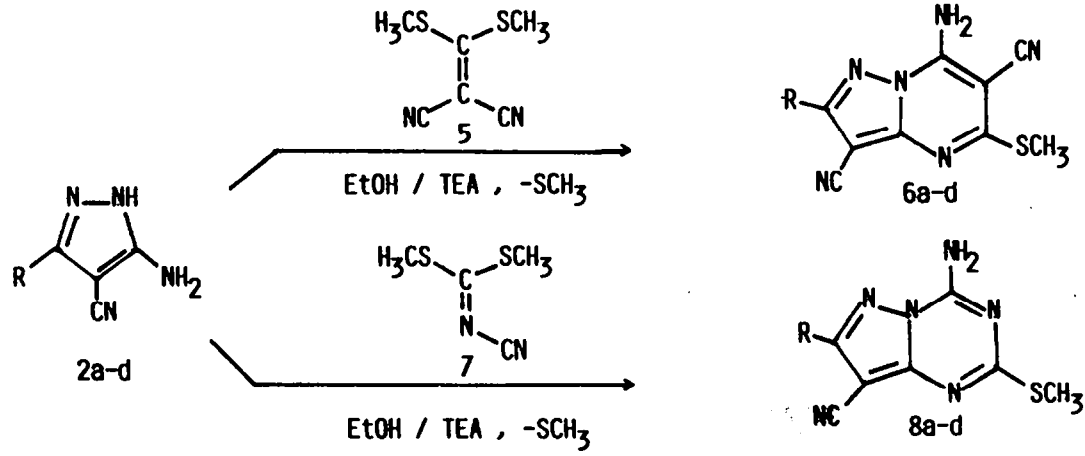


2a,b 3a,b 4a-d

4a : R = NH_2 R` = H 4c : R = $NH_2$ R` = CH_3

4b : R = 2,5-dimethyl-1-pyrryl, R` = H 4d : R = 2,5-dimethyl-1-pyrryl, R` = CH_3

Treatment of 2a-d with 5 leads to the substituted pyrazolo[1,5-a]pyrimidines 6a-d and with 7 to the substituted pyrazolo[1,5-a]1,3,5 triazines 8a-d.



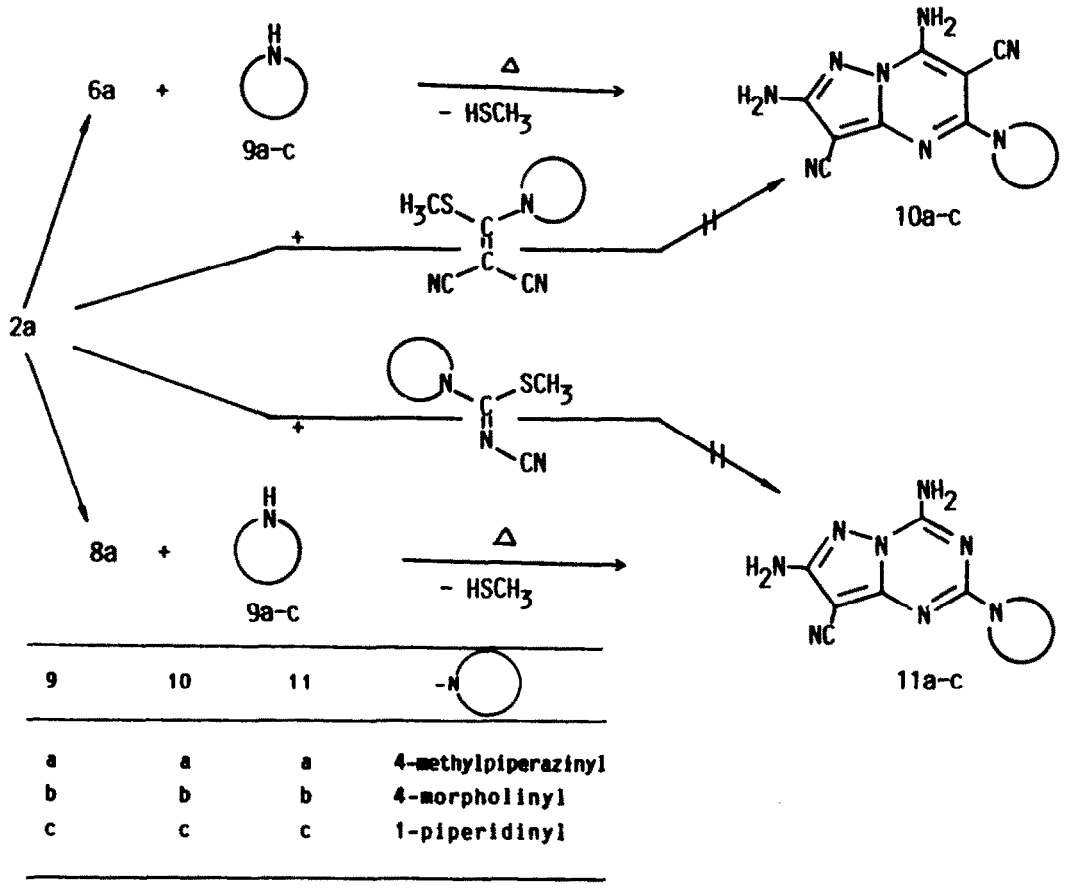
6a, 8a : R = NH_2

6b, 8b : R = 2,5-dimethyl-1-pyrryl

6c, 8c : R = 4-morpholinyl

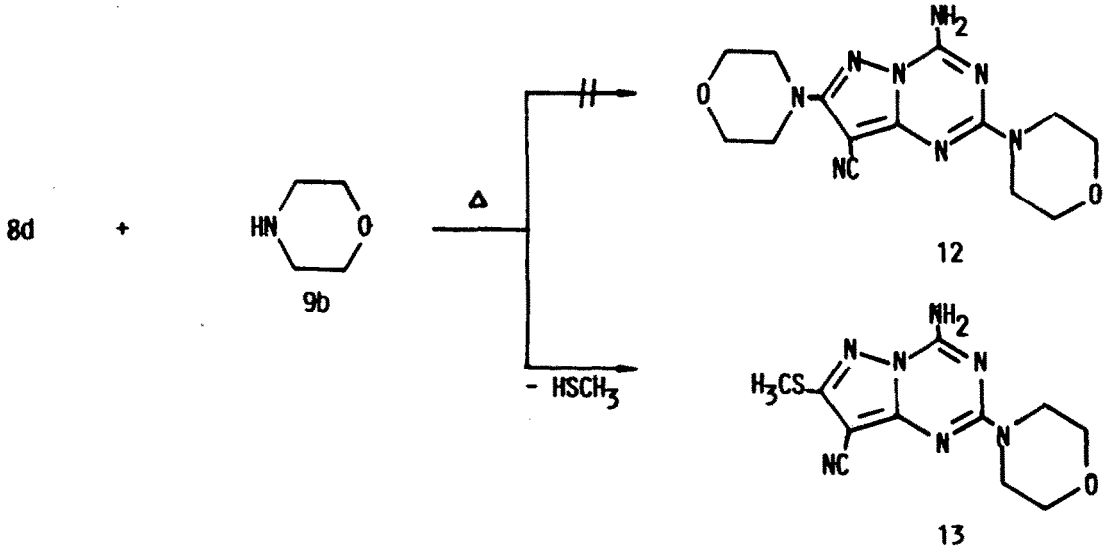
6d, 8d : R = SCH_3

Compounds **6a** and **8a** react with a surplus of the secondary amines **9a-c** to **10a-c** and **11a-c**. The one-step reaction of **2a** with appropriate acrylonitrile or N-cyanoimidate derivates to **10a-c** or **11a-c**, however, was never successful.

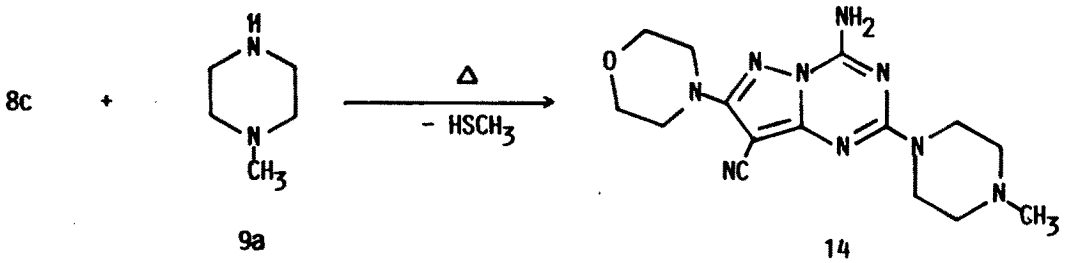


9	10	11	-N
a	a	a	4-methylpiperazinyl
b	b	b	4-morpholinyl
c	c	c	1-piperidinyl

Compound **8a** reacts with morpholine **9b** only to **13** and not to **8c** or **12**. This means that the methylmercapto group can only be substituted by a secondary amine when located on the pyrimidine or triazine and not on the pyrazole part of the ring structure.

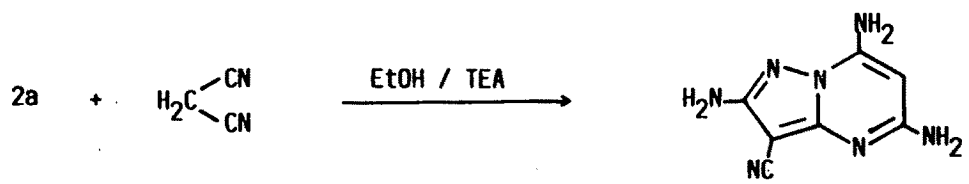


N-methylpiperazine **9a** leads to substitution of the methylmercapto group in the triazine nucleus whereby **14** is produced.



9a **14**

Treatment of **2a** with malonodinitrile **15** allows the separation of substitution product **16**



15 **16**

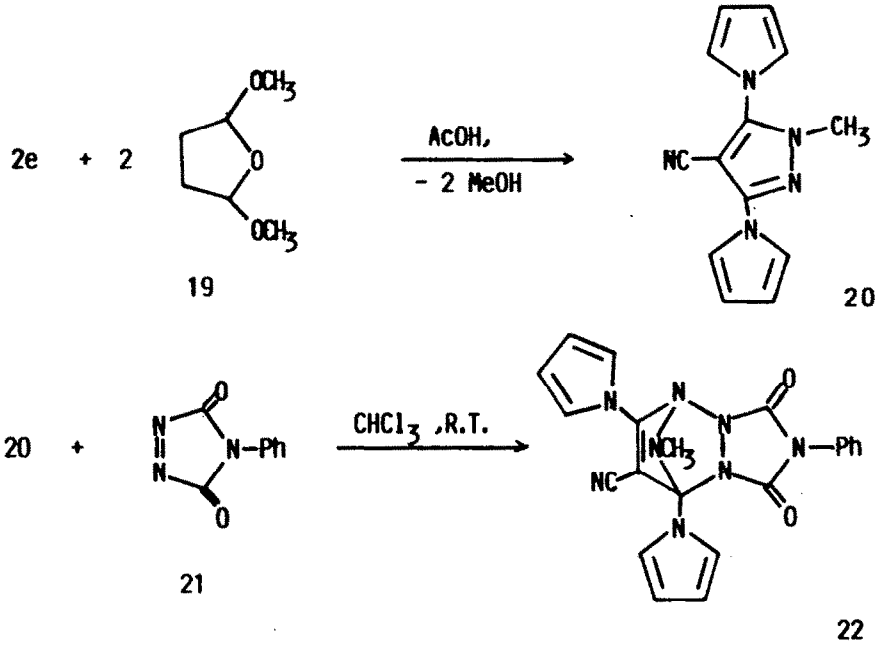
Condensation of aminopyrazoles **2a, 2c** and **2d** with ethylidene-malodinitrile derivatives **17a, 17b** leads to racemic dihydro-pyrazolo[1,5-a]pyrimidines **18a-e.**

17a,b **18a-e**

17	Ar
a	4-chlorophenyl
b	2,6-dichlorophenyl

18	R	Ar
a	NH_2	4-chlorophenyl
b	NH_2	2,6-dichlorophenyl
c	4-morpholinyl	4-chlorophenyl
d	4-morpholinyl	2,6-dichlorophenyl
e	SCH_3	4-chlorophenyl

Reaction of **2e** with 2,5-dimethoxytetrahydrofuran **19** leads to **20**, which can be converted with the heterodienophile **21** via Diels-Alder addition to **22**. Further results on these reactions will be published separately.



EXPERIMENTAL

IR spectra were recorded on Perkin-Elmer 398 spectrophotometer. NMR spectra on a Bruker WH 270. All melting points are uncorrected.

3,5-Diamino-1H-pyrazolo-4-carbonitrile (2a) - To a solution of hydrazine hydrate (10 ml) in ethanol (20 ml) was added 1-amino-1-methylmercapto-2,2-dicyano-ethylene (9.73 g; 0.07 mol). The mixture was stirred under reflux for 2h with evolution of methylmercaptane. Solvent was removed under reduced pressure. The residue was recrystallized from ethanol/ether and obtained as white solid (6.20 g; 72%), m.p.171°- Anal.Calcd. for $C_4H_5N_5$ (123.1): C, 39.02; H, 4.09; N, 56.89. Found. C,38.94; H, 4.12; N, 56.67%.

3,5-Diamino-1-methyl-1H-pyrazolo-4-carbonitrile (2e) - Utilization of methyl hydrazine instead of hydrazine hydrate in the preparation of **2a** leads to compound **2e** (7.0 g; 73%), m.p.202-203°- Anal. Calcd. for $C_5H_7N_5$ (137.2): C, 43.79, H, 5.14; N, 51.07. Found. C, 43.68; H, 5.17; N, 50.96%.

3-Amino-5-(2,5-dimethyl-1-pyrryl)-1H-pyrazolo-4-carbonitrile (2b) - A mixture of **2a** (2.46 g; 0.02 mol) and acetonylacetone (2.28 g; 0.02 mol) in ethanol (20 ml) and acetic acid (20 ml) were stirred under reflux for 2h. The solvent was evaporated and the residue was recrystallized from chloroform/ethyl acetate to give a microcrystalline powder (2.49 g; 62%), m.p.193-194°- Anal. Calcd. for $C_{10}H_{11}N_5$ (201.2): C, 59.69; H, 5.51; N, 34.80. Found. C, 59.39; H, 5.36; N, 34.61% - ^{1}HNMR (DMSO-d6): δ= 12.14 (s, 1H); 6.63 (s, 2H); 5.77 (s, 2H); 2.03 (s, 6H).

General Procedure for the Synthesis of Pyrazolopyrimidines 4a-d; 6a-d and Pyrazolotriazines 8a-d. - A mixture of aminopyrazoles **2a-d** (0.02 mol), equimolar amounts of the ethylene compounds **3a, 3b, 5, 7** and triethylamine (2 ml) in ethanol (50 ml) were stirred under reflux for 2h. After cooling, the precipitate was filtered off and recrystallized (**4a, 4c, 6a** and **6d** from DMF/EtOH; **6c, 8a, 8c** and **8d** from AcOH). In the case of **4b, 4d, 6b** and **8b**, the solvent was removed under reduced pressure and the residue chromatographed on a column of silica gel, elution with a mixture of chloroform/ethyl acetate 3:2. - Recrystallization from ethanol. Data see Table 1 - ^{1}HNMR of compounds: **4c** (DMSO-d6): δ = 8.55 (s, 2H); 6.52 (2, 2H); 2.47 (s, 3H). **6a** (DMSO-d6): δ= 7.65 (s, 2H); 6.65 (s, 2H); 2.88 (s, 3H). **8b** (DMSO-d6): δ= 8.07,7.95 (d, 2H); 5.90,5.88 (d, 2H); 2.64 (s, 3H); 2.12,2.10 (d, 6H).

Table 1.

No.	Product	m.p.[°C] Yield[%]	Molecular formula	Calcd. Found.	Analyses[%] C	H	N
4a	2,4-diamino-pyrazolo[1,5-a]-pyrimidine-3,6-dicarbonitrile	>300,dec. 62	$C_8H_5N_7$	48.24 47.98		2.53 2.65	49.23 48.97
4b	7-amino-2(2,5-dimethyl-1-pyr-ryl)-pyrazolo[1,5-a]pyrimidine-3,6-dicarbonitrile	276,dec. 57	$C_{14}H_{11}N_7$	60.64 60.63		4.00 4.29	35.36 35.11
4c	2,7-diamino-5-methyl-pyrazolo-[1,5-a]pyrimidine-3,6-dicarbo-nitrile	>300,dec. 58	$C_9H_7N_7$	50.70 50.39		3.31 3.36	45.99 45.72
4d	7-amino-2(2,5-dimethyl-1-pyrr-yl)-pyrazolo[1,5-a]pyrimidine	258,dec. 55	$C_{15}H_{13}N_7$	61.85 61.71		4.50 4.53	33.66 33.39
6a	2,7-diamino-5-methylmercapto-pyrazolo[1,5-a]pyrimidine-3,6-dicarbonitrile	>300,dec. 65	$C_9H_7N_7S$	44.07 43.89		2.88 3.14	39.98 40.13
6b	7-amino-2(2,5-dimethyl-1-pyrr-yl)-5-methylmercapto-pyrazolo-[1,5-a]pyrimidine-3,6-dicarbo-nitrile	247,dec. 53	$C_{15}H_{13}N_7S$	55.71 55.50		4.05 4.11	30.32 30.18
6c	7-amino-5-methylmercapto-2-(4-morpholinyl)-pyrazolo - [1,5-a]pyrimidine-3,6-di-carbonitrile	218,dec. 61	$C_{13}H_{13}N_7OS$	49.51 49.67		4.16 4.21	31.09 30.83
6d	7-amino-2,5-dimethylmercapto-pyratolo[1,5-a]pyrimidine-3,6-dicarbonitrile	>300,dec. 62	$C_{10}H_8N_6S_2$	43.46 43.47		2.92 2.89	30.41 30.54
8a	4,7-diamino-2-methylmercapto-pyrazolo[1,5-a]1,3,5 triazine-8-carbonitrile	>300,dec. 65	$C_7H_7N_7S$	38.00 37.72		3.19 3.29	44.31 44.06
8b	4-amino-7(2,5-dimethyl-1-pyrr-yl)-2-methylmercapto-pyrazolo-[1,5-a]1,3,5 triazine-8-carbo-nitrile	245,dec. 54	$C_{13}H_{13}N_7S$	52.16 52.21		4.38 4.43	32.75 32.59
8c	4-amino-2-methylmercapto-7-(4-morpholinyl)-pyrazolo-[1,5-a]1,3,5 triazine-8-carbonitrile	300-301 62	$C_{11}H_{13}N_7OS$	45.35 45.09		4.50 4.42	33.66 33.44
8d	4-amino-2,7-dimethylmercapto-pyrazolo[1,5-a]1,3,5 triazine-8-carbonitrile	289-290 68	$C_8H_8N_6S_2$	38.08 38.25		3.20 3.23	33.31 33.24

Diaminopyrazolopyrimidines 10a-c. - A mixture of pyrazolopyrimidine **6a** (1.23 g; 5 mmol) in amines **9a-c** (15 ml) was refluxed for 2h. The solvent was removed under reduced pressure and the residue was recrystallized from acetic acid. The physical properties are reported in Table 2.

Diaminopyrazolotriazines 11a-c. - Compounds **11a-c** were prepared similarly using pyrazolotriazine **8a** and amines **9a-c**. The physical properties are collected in Table 2.

4-Amino-7-methylmercapto-2-(4-morpholinyl)-pyrazolo[1,5-a]1,3,5 triazine-8-carbonitrile(13) - Compound **13** prepared in a similar manner from pyrazolotriazine **8d** and morpholine, was recrystallized from DMF (1.31 g; 90%), m.p.285°C, dec. - Anal.Calcd. for $C_{11}H_{13}N_7OS$ (291.3): C, 45.35; H, 4.50; N, 33.66. Found. C, 45.38; H, 4.56; N, 33.38% - ^{1}HNMR (DMSO-d6): δ= 7.38,7.22 (d, 2H); 4.15 (s, 4H); 3.74 (s, 4H); 2.53 (s, 3H).

4-Amino-2(4-methylpiperazinyl)-7(4-morpholinyl)-pyrazolo[1,5-a]1,3,5 triazine-8-carbonitrile (14) - Compound **14** prepared in a similar manner from pyrazolotriazine **8c** and N-methylpiperazine, Compound **14** was obtained from AcOH as white microcrystalline, (1.48 g; 86%), m.p. 270°C, dec. - Anal. Calcd. for $C_{15}H_{21}N_9O$ (343.4): C, 52.47; H, 6.16; N, 36.71. Found. C, 52.45; H, 6.06; N, 36.71% - ^{1}HNMR (DMSO-d6): δ= 7.18, 7.10 (d, 2H); 4.12 (s, 4H); 3.75 (s, 4H); 3.46 (s, 4H); 2.42 (s, 4H); 2.23 (s, 3H)

2,5,7-Triamino-pyrazolo[1,5-a]pyrimidine-3-carbonitrile (16) - A mixture of **2a** (1.23 g; 10 mmol), malononitrile (0.66 g; 10 mmol) and triethylamine (1 ml) in EtOH (50 ml) were stirred at room temperature for 24h and 1h under reflux. After cooling, the precipitate was filtered off and recrystallized from DMF (0.93 g; 49%), m.p. >300°C, dec. - Anal. Calcd. for $C_7H_7N_7$(189.2): C, 44.44; H, 3.73; N, 51.83. Found. C, 44.22; H, 3.78; N, 51.71% - ^{1}HNMR (DMSO-d6): δ = 6.84,6.77 (d, 2H); 6.41 (s, 2H); 5.90,5.77 (d, 2H); 5.24 (s, 1H).

Table 2.

No.	Product	m.p.[°C] Yield[%]	Molecular formula	Calcd. Found.	Analyses[%] C	H	N
10a	2,7-diamino-5(4-methyl-1-piperazinyl)-pyrazolo[1,5-a]pyrimidine-3,6-dicarbonitrile	293,dec. 75	$C_{13}H_{15}N_9$		52.52 52.23	5.09 5.13	42.40 42.17
10b	2,7-diamino-5(4-morpholinyl)-pyrazolo[1,5-a]pyrimidine-3,6-dicarbonitrile	>300,dec. 78	$C_{12}H_{12}N_8O$		50.70 50.74	4.25 4.32	39.42 39.16
10c	2,7-diamino-5(1-piperidinyl)-pyrazolo[1,5-a]pyrimidine-3,6-dicarbonitrile	>300,dec. 76	$C_{13}H_{14}N_8$		55.31 55.07	5.00 4.94	39.69 39.93
11a	4,7-diamino-2(4-methyl-1-piperazinyl)-pyrazolo[1,5-a]1,3,5-triazine-8-carbonitrile	292,dec. 78	$C_{11}H_{15}N_9$		48.34 48.27	5.53 5.55	46.13 45.95
11b	4,7-diamino-2(4-morpholinyl)-pyrazolo[1,5-a]1,3,5 triazine-8-carbonitrile	>300,dec. 80	$C_{10}H_{12}N_8O$		46.15 46.07	4.88 4.70	43.05 42.81
11c	4,7-diamino-2(1-piperidinyl)-pyrazolo[1,5-a]1,3,5 triazine-8-carbonitrile	276,dec. 70	$C_{11}H_{14}N_8$		51.15 51.00	5.46 5.49	43.38 43.36

General Procedure for Preparing of Dihydropyrazolopyrimidines 18a-e. - A mixture of **2a, 2c, 2d** (10 mmol), equimolar amounts of the ethylidene compounds **17a, 17b** and triethylamine (1 ml) in ethanol (50 ml) were stirred at room temp. for 24h and stirred under reflux for 1h. After cooling, the precipitate was filtered off, and recrystallized from AcOH/EtOH. The physical properties are reported in Table 3. - ^{1}HNMR of **18d** (DMSO-d6): δ = 8.92 (s, 1H); 7.58-7.37 (m, 3H); 6.95 (s, 2H); 6.32 (s, 1H); 3.73 (s, 4H); 3.34 (s, 4H).

1-Methyl-3,5-di-1-pyrryl-1H-pyrazole-4-carbonitrile (20) - A mixture of **2e** (2.74 g; 20 mmol), 2,5-dimethoxytetrahydrofuran (5.28 g; 40 mmol), in acetic acid (30 ml) were stirred under reflux for 1h. The solvent was removed under reduced pressure and the residue chromatographed on a column of silica gel, elution with a mixture of chloroform/ethyl acetate 9:1. Recrystallization from chloroform/ethanol 1:2 (3.27 g; 69%) m.p.104°C. - Anal. Calcd. for $C_{13}H_{11}N_5$ (237.3): C, 65.81; H, 4.67; N, 29.52. Found. C, 65.70; H, 4.76; N, 29.44%

10-Methyl-6,8-dioxo-7-phenyl-2,4-di-1-pyrryl-1,4,7,8-tetrahydro-6H-1,4-epimino-[1,2,4]triazolo[1,2-a][1,2,3]triazine-3-carbonitrile (22) - To a solution of **20** (0.71g; 3 mmol) in chloroform (40 ml) was added **21** (0.51 g; 2.9 mmol). The mixture was stirred at room temp. 1h. The solvent was removed under reduced pressure and the residue chromatographed on a columen of silica gel, elution with a mixture of n-hexane/ethyl acetate 2:1. Recrystallization from ethyl acetate as white microcrystalline (0.74 g; 62%) m.p.125°C, dec. - Anal. Calcd. for $C_{21}H_{16}N_8O_2$ (412.7): C, 61.16; H, 3.91; N, 27.17. Found. C, 61.20; H, 3.87; N, 26.87% - ^{1}HNMR ($CDCl_3$): δ = 7.60-7.25 (m, 7H); 6.94 (t, 2H); 6.58 (q, 1H); 6.47 (t, 2H); 6.40 (t, 1H).

Table 3.

No.	Product	m.p.[°C] Yield[%]	Molecular formula	Calcd. Found.	Analyses[%] C	H	N
18a	2,7-diamino-5-(4-chlorophenyl)-4,5-dihydro-pyrazolo[1,5-a]-pyrimidine-3,6-dicarbonitrile	>300,dec. 57	$C_{14}H_{10}ClN_7$	53.94 53.74	3.23 3.22	31.45 31.21
18b	2,7-diamino-5-(2,6-dichlorophenyl)-4,5-dihydro-pyrazolo[1,5-a]-pyrimidine-3,6-dicarbonitrile	263,dec. 60	$C_{14}H_9Cl_2N_7 \cdot \frac{1}{2}H_2O$	47.34 47.62	2.84 2.99	27.60 27.34
18c	7-amino-5-(4-chlorphenyl)-2-(4-morpholinyl)-4,5-dihydro-pyrazolo[1,5-a]pyrimidine-3,6-dicarbonitrile	293,dec. 56	$C_{18}H_{16}Cl\,N_7O \cdot \frac{1}{2}H_2O$	55.32 55.03	4.38 4.15	25.09 24.83
18d	7-amino-5-(2,6-dichlorophenyl)-2-(4-morpholinyl)-4,5-dihydro-pyrazolo[1,5-a]pyrimidine-3,6-dicarbonitrile	298,dec. 52	$C_{18}H_{15}Cl_2N_7O$	51.94 51.68	3.63 3.60	23.55 23.48
18e	7-amino-5-(4-chlorophenyl)-2-methylmercapto-4,5-dihydro-pyrazolo[1,5-a]pyrimidine-3,6-dicarbonitrile	261,dec. 64	$C_{15}H_{11}ClN_6S$	52.56 52.36	3.23 3.31	24.52 24.27

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