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SYNTHESIS OF SOME NEW SPIROPYRAZOLO[4',5' :5,6]-PYRANO [2,3-*d*] PYRIMIDINES

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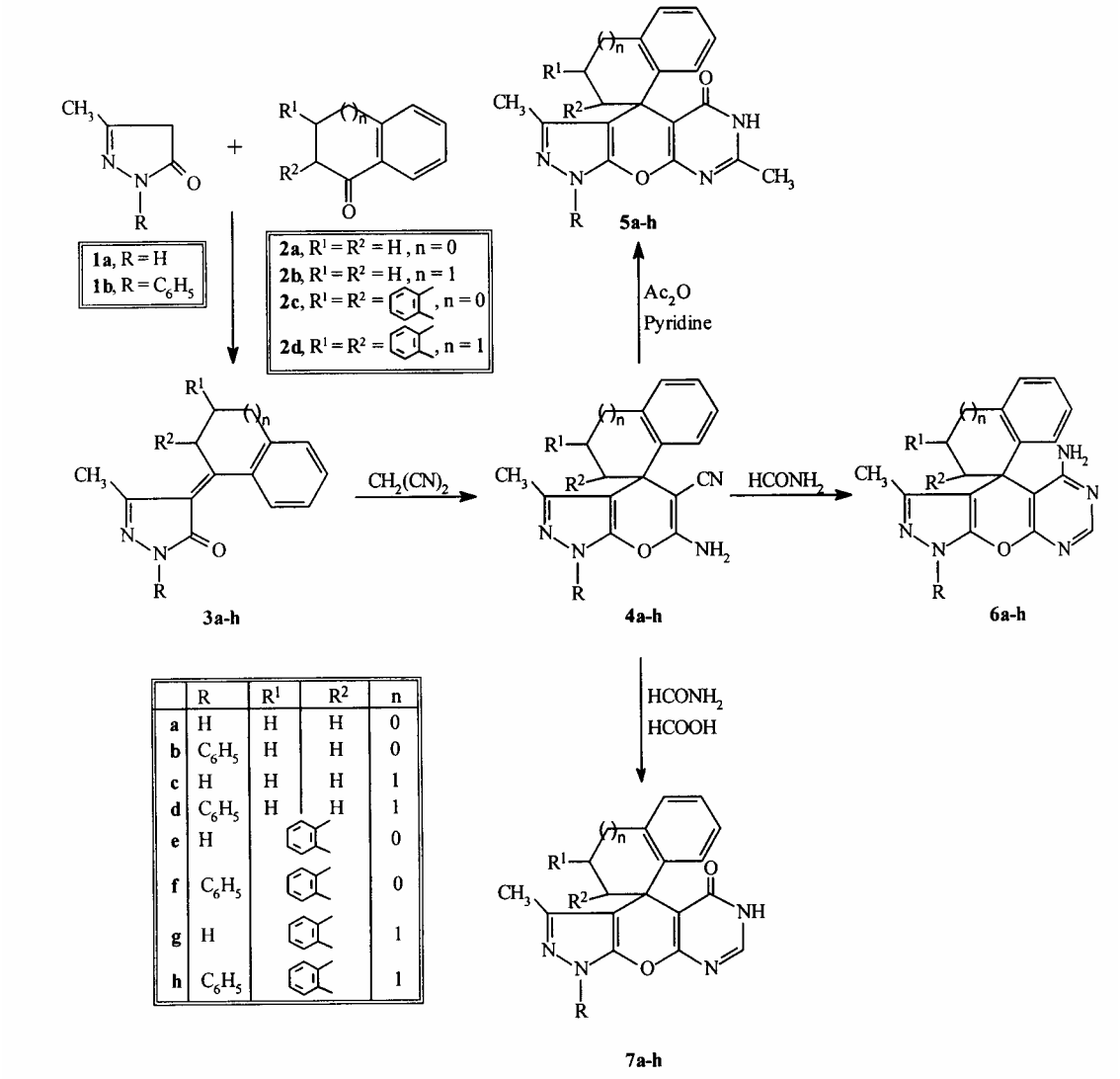
Abstract - 3-Methylpyrazolin-5-ones **(1a,b)** were reacted with cycloalkpyranones **(2a-d)** in the presence of fused sodium acetate to give the corresponding cycloalkylidene derivatives **(3a-h)**. Reaction of compounds **(3a-h)** with malononitrile gave the pyrano derivatives **(4a-h)**, which were cyclized to pyranopyrimidines with acetic anhydride/pyridine, formamide and formamide/formic acid.

Nitriles were used as starting materials to prepare a viarity of condensed pyrans[1-5] for their medicinal Importance.[6,7] Spiro derrvatrves have anticonvulant antibactenal antitubercula and anticancer actrvrtres.[8,9] Also spiroheterocycles were used as nitric oxide synthesis inhibitors,[10] photoisomerization [11,12] and potential topical agents for vaginal infection.[13] It is of interest to note that pyrazoles are reported as well pharmaceuticals[14-17] and pyrimidines derivatives have been used as adenosine kinase inhibitors.[18] From this point of view and in continuation to our previous work,[19-28] we report herein the synthesis of spiropyrazolo[4',5':5,6]pyrano[2,3-*d*]pyrimidines in the hope that members of them could fmd interesting biological applications.

3-Methyl-4-cycloalkylidenepyrazolin-5-ones **(3a-h)** were prepared by the reaction of 3-methylpyrazolin-5-ones **(la,b)** with 1 -indanone **(2a)**, 1 -tetralone **(2b)**, fllourenone **(2c)** and anthrpyranone **(2d)** in the presence of fused sodium acetate. The structures of compounds **(3a-h)** were established from their elemental analyses and spectroscopic data (Table 1). The IR spectrum of **3b** showed absorption band at 1710 cm^{-1} for the carbonyl group of pyrazoline ring. The ^{1}H-NMR spectrum of **3b** (DMSO-d_6) showed the following signals: δ 2.30 (3H, s, CH_3 group at C_3 of the pyrazoline ring), 2.40-2.50 (4H, m, 2 CH_2 groups of indan ring) and 7.00-8.15 (9H, m, the aromatic protons of the phenyl group at the nitrogen of the pyrazolinone moiety and the indan protons). The MS spectrum of **3b** showed the molecular ion peak at (m/z, o/o relative intensity) 288 (100) and the following fragments: 217 (2), 174 (90), 132 (20), 1 15 (30), 91 (70), 77 (95).

It is pertinent to mention here that compounds **(3a-d)** where formed to be mixture of two geometrica isomers, Z and E.[29] The major *E* were purified and were reacted with malononitrile. Reaction of **3a-h** with malononitrile in ethanol in the presence of piperidine as a basic catalyst gave the corresponding pyrano[2,3-*c*]pyrazole **(4a-h)** (Scheme 1).



	R	R^1	R^2	n
a	H	H	H	0
b	C_6H_5	H	H	0
c	H	H	H	1
d	C_6H_5	H	H	1
e	H			0
f	C_6H_5			0
g	H			1
h	C_6H_5			1

Scheme 1

The IR spectrum of **4b** showed the following characteristic absorption bands at 2200 cm^{-1} (CN); 3040, 3140 cm^{-1} (NH_2). The ^{1}H-NMR ($CDC1_3$) spectrum showed the following signals: δ 2.40-2.60 (4H, m, 2 CH_2), 2.25 (3H, s, CH_3), 9.80 (2H, s, NH_2), 7.00-8.20 (9H, m, arom.).

Reaction of 6-amino-5-cyano-3-methyl- 4 -spiropyrano[2,3-*c*]pyrazole **(4a-h)** with acetic anhydrid/ pyridine

mixture, formamide and formamide/formic acid mixture gave the corresponding 3,5-dimethyl-6(*H*)-5oxo-4-spiropyrazolo[4',5':5,6]pyrano[2,3-*d*]pyrimidines **(5a-h)**, 5-amino-3 -methyl-4-spiropyrazolo [4',5': 5,6]pyrano-[2,3-*d*]pyrimidines**(6a-h)** and 3-methyl-6(*H*)-5-oxo-4-spiropyrazolo[4',5':5,6]-pyrano[2,3-*d*]pyrimidines **(7a-h)** respectively. The ^{1}H-NMR spectrum showed the following signals: δ 2.50-2.80 (6H, m, 3 CH_2), 2.30 (3H, s, CH_3), 3.30 (3H, s, CH_3), 7.00-8.20 (9H, m, arom) for **5d**; 2.40 (3H, s, CH_3), 9.80 (2H s NH_2), 7 20-8.50 (14H, m, arom) for **6f** and 2 35 (3H, s, CH_3), 2 90 (2H, s, CH_2), 7 20 8 60 (14H, s, arom.) for **7h** respectively. The physical properties and spectral data are given in Table 1 .

Table 1. Physical and Spectral Data of Spiropyrazolinones **(3a-h)**, Spiropyrazolopyrans **(4a-h)** and Spiropyrazolo[4',5':5,6]pyrano[2,3-*d*]pyrimidines **(5a-h; 7a-h)**

Compd No.	Yield (%)	mp (°C)	Molecular Formula (Solvent of Recrystallization)	IR (υ, cm^{-1}) (KBr)	NMR (δ, ppm) (Solvent)	*Anal.* Calcd/(Found) % C	H	N
3a	86	220-222	$C_{13}H_{12}N_2O$ (ethanol)	3200 (NH), 1720 (C=O)	(DMSO-d_6): 2.25 (3H, s), 2.40-2.50 (4H, m), 5.80 (1H, s), 7.00-7.80 (4H, m)	73.57 (73.40)	5.70 (5.50)	13.20 (13.15)
3b	90	180-182	$C_{19}H_{16}N_2O$ (ethanol)	1710 (C=O)	(DMSO-d_6): 2.30 (3H, s), 2.40-2.50 (4H, m), 7.00-8.15 (9H, m)	79.14 (79.10)	5.59 (5.50)	9.72 (9.60)
3c	82	125-127	$C_{14}H_{14}N_2O$ (ethanol)	3210 (NH), 1680 (C=O)	(DMSO-d_6): 1.80-2.10 (2H, m), 2.25 (3H, s),2.50 (2H, t, *J* = 4.5 Hz), 2.80 (2H, t, *J* = 4.7 Hz), 5.80 (1H, s), 7.00-7.80 (4H, m)	74.31 (74.20)	6.24 (6.10)	12.38 (12.20)
3d	88	240-242	$C_{20}H_{18}N_2O$ (ethanol)	1710 (C=O)	(DMSO-d_6): 1.80-2.10 (2H, m), 2.30 (3H, s),2.50 (2H, t, *J* = 4.5 Hz), 2.80 (2H, t, *J* = 4.7 Hz), 7.00-8.20 (9H, m)	79.44 (79.40)	6.00 (5.80)	9.27 (9.18)
3e	78	210-212	$C_{17}H_{12}N_2O$ (ethanol)	3276 (NH), 1685 (C=O)	(DMSO-d_6): 2.27 (3H, s), 5.75 (1H, s), 7.00-8.20 (8H, m)	78.44 (78.40)	4.65 (4.50)	10.76 (10.55)
3f	85	200-202	$C_{23}H_{16}N_2O$ (ethanol)	1710 (C=O)	(DMSO-d_6): 2.30 (3H, s), 7.00-8.20 (13H, m)	82.12 (82.10)	4.79 (4.70)	8.33 (8.20)
3g	75	180-182	$C_{18}H_{14}N_2O$ (ethanol)	3175 (NH), 1685 (C=O)	(DMSO-d_6): 2.30 (3H, s), 2.80 (2H, s), 5.75 (1H, s), 7.00-8.20 (8H, m)	78.81 (78.70)	5.14 (5.00)	10.21 (10.10)
3h	80	230-232	$C_{24}H_{18}N_2O$ (ethanol)	1710 (C=O)	(DMSO-d_6): 2.30 (3H, s), 2.80 (2H, s), 7.00-8.10 (13H, m)	82.26 (82.20)	5.18 (5.10)	7.99 (7.97)
4a	75	238-240	$C_{16}H_{14}N_4O$ (dioxane)	3180 (NH), 3080, 3150 (NH_2), 2200 (CN), 1610 (C=N)	($CDCl_3$): 2.40-2.60 (4H, m), 2.25 (3H, s), 8.60 (1H, s), 9.80 (2H, s), 7.00-8.10 (4H, m)	69.05 (69.14)	5.07 (5.11)	20.13 (20.22)
4b	70	151-153	$C_{22}H_{18}N_4O$ (dioxane)	3040,3140 (NH_2), 2200 (CN), 1600 (C=N)	($CDCl_3$): 2.40-2.60 (4H, m), 2.25 (3H, s), 9.80 (2H, s), 7.00-8.20 (9H, m)	74.56 (74.65)	5.12 (5.07)	15.81 (15.76)
4c	67	208-210	$C_{17}H_{16}N_4O$ (dioxane)	3180 (NH), 3050, 3150 (NH_2), 2220 (CN), 1600 (C=N)	($CDCl_3$): 2.40-2.80 (6H, m), 2.30 (3H, s), 8.80 (1H, s), 9.70 (2H, s), 7.10-8.30 (4H, m)	69.85 (69.93)	5.52 (5.44)	19.16 (19.24)

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Table 1. ***(Continued)*** Physical and Spectral Data of Spiropyrazolinones **(3a-h)**, Spiropyrazolopyrans **(4a-h)** and Spiropyrazolo[4',5':5,6]pyrano[2,3-*d*]pyrimidines **(5a-h; 7a-h)**

Compd No.	Yield (%)	mp (°C)	Molecular Formula (Solvent of Recrystallization)	IR (υ, cm^{-1}) (KBr)	NMR (δ, ppm) (Solvent)	*Anal.* Calcd/(Found) % C	H	N
4c	67	208-210	$C_{17}H_{16}N_4O$ (dioxane)	3180 (NH), 3050, 3150 (NH_2), 2220 (CN), 1600 (C=N)	($CDCl_3$): 2.40-2.80 (6H, m), 2.30 (3H, s), 8.80 (1H, s), 9.70 (2H, s), 7.10-8.30 (4H, m)	69.85 (69.93)	5.52 (5.44)	19.16 (19.24)
4d	39	138-140	$C_{23}H_{20}N_4O$ (dioxane)	3060,3160 (NH_2), 2220 (CN), 1600 (C=N)	($CDCl_3$): 2.30 (3H, s), 2.40-2.80 (6H, m), 7.20-8.30 (9H, m), 9.80 (2H, s)	74.98 (74.87)	5.47 (5.54)	15.21 (15.30)
4e	66	220-222	$C_{20}H_{14}N_4O$ (dioxane)	3200 (NH), 3060, 3160 (NH_2), 1610 (C=N)	(CF_3COOD): 2.30 (3H, s), 7.10-8.40 (8H, m)	73.60 (73.52)	4.32 (4.26)	17.17 (17.25)
4f	68	187-189 (decomp)	$C_{26}H_{18}N_4O$ (dioxane)	3050,3150 (NH_2), 1600 (C=N)	(CF_3COOD): 2.40 (3H, s), 6.90-8.20 (13H, m)	77.60 (77.68)	4.51 (4.44)	13.92 (13.85)
4g	73	210-212	$C_{21}H_{16}N_4O$ (dioxane)	3190 (NH), 3050, 3150 (NH_2), 1600 (C=N)	($CDCl_3$): 2.30 (3H, s), 2.60 (2H, s), 7.10-8.20 (8H, m), 8.60 (1H, s), 9.90 (2H, s)	74.10 (74.21)	4.74 (4.69)	16.46 (16.52)
4h	76	158-160	$C_{27}H_{20}N_4O$ (dioxane)	3060,3160 (NH_2), 1600 (C=N)	($CDCl_3$): 2.30 (3H, s), 2.70 (2H, s), 7.10-8.30 (9H, m), 10.10 (13H, s)	77.87 (77.75)	4.84 (4.91)	13.45 (13.51)
5a	61	> 320	$C_{18}H_{16}N_4O_2$ (ethanol)	3160 (NH), 1690 (C=O)	(CF_3COOD): 2.25 (3H, s), 2.40-2.60 (4H, m), 3.10 (3H, s), 6.90-7.70 (4H, m)	67.49 (67.58)	5.03 (5.11)	17.49 (17.41)
5b	63	292-294	$C_{24}H_{20}N_4O_2$ (ethanol)	3150 (NH), 1690 (C=O)	(CF_3COOD): 2.30 (3H, s), 2.50-2.60 (4H, m), 3.20 (3H, s), 7.10-8.20 (9H, m)	72.71 (72.65)	5.08 (5.12)	14.13 (14.19)
5c	58	271-273	$C_{19}H_{18}N_4O_2$ (ethanol)	3220 (NH), 1680 (C=O)	(CF_3COOD): 2.30 (3H, s), 2.50-2.80 (6H, m), 3.20 (3H, s), 7.00-7.90 (4H, m)	68.25 (68.33)	5.43 (5.51)	16.67 (16.68)
5d	66	186-188	$C_{25}H_{22}N_4O_2$ (ethanol)	3230 (NH), 1710 (C=O)	(CF_3COOD): 2.30 (3H, s), 2.50-2.80 (6H, m), 3.30 (3H, s), 7.00-8.20 (9H, m)	73.15 (73.21)	5.40 (5.35)	13.65 (13.74)
5e	71	258-260	$C_{22}H_{16}N_4O_2$ (ethanol)	3270 (NH), 1690 (C=O)	(CF_3COOD): 2.30 (3H, s), 3.30 (3H, s), 7.00-8.10 (8H, m)	71.73 (71.83)	4.38 (4.42)	15.21 (15.14)
5f	74	216-218	$C_{28}H_{20}N_4O_2$ (ethanol)	3290 (NH), 1710 (C=O)	(CF_3COOD): 2.35 (3H, s), 3.40 (3H, s), 7.00-8.40 (13H, m)	75.66 (75.78)	4.54 (4.48)	12.60 (12.72)
5g	65	165-167 (decomp)	$C_{23}H_{18}N_4O_2$ (ethanol)	3300 (NH), 1695 (C=O)	(CF_3COOD): 2.30 (3H, s), 2.90 (2H, s), 3.20 (3H, s), 7.10-8.40 (8H, m)	72.24 (72.29)	4.74 (4.68)	14.65 (14.77)
5h	70	108-110 (decomp)	$C_{29}H_{22}N_4O_2$ (ethanol)	3290 (NH), 1700 (C=O)	(CF_3COOD): 2.30 (3H, s), 2.80 (2H, s), 3.20 (3H, s), 7.20-8.60 (13H, m)	75.97 (75.89)	4.84 (4.77)	12.22 (12.31)
6a	70	> 320	$C_{17}H_{15}N_5O$ (dioxane)	3180 (NH), 3050, 3150 (NH_2)	(CF_3COOD): 2.30 (3H, s), 2.40-2.60 (4H, m), 6.90-7.90 (5H, m)	66.87 (66.94)	4.95 (5.01)	22.94 (23.01)

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Table 1. ***(Continued)*** Physical and Spectral Data of Spiropyrazolinones **(3a-h)**, Spiropyrazolopyrans **(4a-h)** and Spiropyrazolo[4',5':5,6]pyrano[2,3-*d*]pyrimidines **(5a-h; 7a-h)**

Compd No.	Yield (%)	mp (°C)	Molecular Formula (Solvent of Recrystallization)	IR (υ, cm^{-1}) (KBr)	NMR (δ, ppm) (Solvent)	*Anal.* Calcd/(Found) % C	H	N
6b	65	256-258	$C_{23}H_{19}N_5O$ (dioxane)	3060,3160 (NH_2)	(CF_3COOD): 2.30 (3H, s), 2.50-2.60 (4H, m), 7.10-8.20 (10H, m)	72.42 (72.34)	5.02 (5.11)	18.36 (18.43)
6c	61	268-270	$C_{18}H_{17}N_5O$ (dioxane)	3180 (NH), 3050, 3150 (NH_2)	(CF_3COOD): 2.30 (3H, s), 2.50-2.80 (6H, m), 7.10-8.30 (5H, m)	67.70 (67.58)	5.37 (5.94)	21.93 (21.10)
6d	57	168-170	$C_{24}H_{21}N_5O$ (dioxane)	3050,3150 (NH_2)	(CF_3COOD): 2.30 (3H, s), 2.50-2.80 (6H, m), 7.20-8.50 (10H, m)	72.89 (72.61)	5.35 (5.31)	17.71 (17.65)
6e	63	156-158	$C_{21}H_{15}N_5O$ (dioxane)	3180 (NH), 3060, 3160 (NH_2)	(CF_3COOD): 2.30 (3H, s), 7.20-8.40 (9H, m)	71.38 (71.44)	4.28 (4.33)	19.82 (19.79)
6f	57	228-230	$C_{27}H_{19}N_5O$ (dioxane)	3050,3150 (NH_2)	($CDCl_3$): 2.40 (3H, s), 7.20-8.50 (14H, m), 9.80 (2H, s)	75.51 (75.42)	4.46 (4.51)	16.31 (16.28)
6g	51	118-120	$C_{22}H_{17}N_5O$ (dioxane)	3180 (NH), 3070, 3170 (NH_2)	($CDCl_3$): 2.40 (3H, s), 2.70 (2H, s), 7.10-8.30 (9H, m), 8.90 (1H, s), 10.00 (2H, s)	71.92 (71.84)	4.66 (4.51)	19.06 (19.14)
6h	61	130-132	$C_{28}H_{21}N_5O$ (dioxane)	3060,3160 (NH_2)	($CDCl_3$): 2.30 (3H, s), 2.80 (2H, s), 7.20-8.60 (14H, m), 8.80 (1H, s), 10.10 (2H, s)	75.83 (75.73)	4.77 (4.81)	15.79 (15.74)
7a	74	225-227	$C_{17}H_{14}N_4O_2$ (dioxane)	3190 (NH), 1700 (C=O)	(CF_3COOD): 2.30 (3H, s), 2.45-2.60 (4H, m), 6.90-7.80 (5H, m)	66.66 (66.72)	4.61 (4.55)	18.29 (18.22)
7b	56	185-187 (decomp)	$C_{23}H_{18}N_4O_2$ (dioxane)	3200 (NH), 1720 (C=O)	($CDCl_3$): 2.30 (3H, s), 2.50-2.70 (4H, m), 7.10-8.30 (10H, m), 8.70 (1H, s)	72.24 (72.34)	4.74 (4.71)	14.65 (14.73)
7c	63	> 320	$C_{18}H_{16}N_4O_2$ (dioxane)	3200 (NH), 1700 (C=O)	(CF_3COOD): 2.35 (3H, s), 2.40-2.70 (6H, m), 7.20-8.10 (5H, m)	67.49 (67.59)	5.03 (5.13)	17.49 (17.36)
7d	55	155-157 (decomp)	$C_{24}H_{20}N_4O_2$ (dioxane)	3190 (NH), 1700 (C=O)	($CDCl_3$): 2.30 (3H, s), 2.40-2.60 (6H, m), 7.20-8.60 (10H, m), 8.70 (1H, s)	72.71 (72.83)	5.08 (5.14)	14.13 (14.21)
7e	61	143-145 (decomp)	$C_{21}H_{14}N_4O_2$ (dioxane)	3200 (NH), 1710 (C=O)	(CF_3COOD): 2.30 (3H, s), 7.20-8.40 (9H, m)	71.18 (71.29)	3.98 (3.92)	15.81 (15.76)
7f	64	228-230	$C_{27}H_{18}N_4O_2$ (dioxane)	3190 (NH), 1700 (C=O)	($CDCl_3$): 2.30 (3H, s), 7.10-8.30 (14H, m), 8.70 (1H, s)	75.34 (75.43)	4.21 (4.16)	13.02 (13.11)
7g	71	178-180	$C_{22}H_{16}N_4O_2$ (dioxane)	3200 (NH), 1710 (C=O)	(CF_3COOD): 2.95 (2H, s), 2.30 (3H, s), 7.10-8.40 (9H, m)	71.73 (71.81)	4.38 (4.41)	15.21 (15.12)
7h	66	185-187 (decomp)	$C_{28}H_{20}N_4O_2$ (dioxane)	3200 (NH), 1700 (C=O)	(CF_3COOD): 2.90 (2H, s), 2.35 (3H, s), 7.20-8.60 (14H, m)	75.66 (75.51)	4.54 (4.61)	12.60 (12.67)

Antimicrobial Activity

The antimicrobial activity of the newly synthesized compounds was tested against *Staphylococcus aureus DSM 346* and *Escherichia coli DSM 423* using the agar cup diffusion technique.[30] Results of the screened compounds show no inhibition to the organisms tested at a concentration of 20 μg cm^{-1} relative to tetracycline, Only compounds **(5f,6h)** and **(7d,7f)** exhibited moderate activity against *Staphylococcus aureus DSM 346* and *Escherichia coli DSM 423* respectively.

EXPERIMENTAL

The time required for completion ofthe reaction was monitored by TLC. Melting points were determined in open glass cappillaries and are uncorrected. IR (υ, cm^{-1}) spectra were recorded on a Pye-Unicam SP 200-G spectrophotometer. NMR (δ, ppm) spectra were measured on EM-360 90-MHz spectrometer using TMS as internal standard. Elemental analyses were carried out on a Perkin Elmer 240 C microanalyser. MS spectra were recorded on Jeol JMS 600 instrument.

Synthesis of 3-Methyl-4-cycloalkylidenepyrazolin-5-ones **(3a-h)**

General Procedure :

A mixture of 3-methylpyrazolin-5-ones **(1a,b)** (0.01 mol) and the appropriate cyclic ketone **(2a-d)** (0.012 mol) was fused in the presence of anhydrous sodium acetate (1.00 g, 0.012 mol) for 30 min, at 200 ℃. The reaction mixture was allowed to cool, poured into water (200 mL) , whereby the products were precipitated, filtered and crystallized from ethanol (Table 1).

6-Amino-5-cyano-3-methyl-4-spiropyrano[2, 3-*c*]pyrazole **(4a-h)**

General Procedure:

A mixture of 3-methyl-4-cycloalkylidenepyrazolin-5-ones **(3a-h)** (0.01 mol), malononitrile (0.66 g, 0.01 mol) in absolute ethanol (60 mL) and piperidine (1 mL) was heated under reflux for 10 h, then concentrated to half of its volume under reduced pressure and allowed to cool to rt. The product was collected by filtration and recrystallized from dioxane (Table 1).

3 5-Dimethyl-6(*H*)-5-oxo-4-spiropyrazolo[4',5':5,6]pyrano[2,3-*d*]pyrimidines **(5a-h)**

General Procedure:

A solution of **4a-h** (0.01 mol) in acetic anhydride/pyridine mixture (20 mL, 2: I v/v) was heated at 90℃ on a steam bath for 12 h, then cooled and poured into an ice/water mixture. The solid product thus formed was filtered off and washed several times with water and recrystallized from ethanol.

5-Amino-3-methyl-4-spiropyrazolo[4',5':5,6]pyrano[2,3-*d*]pyrimidines (**6a-h**)

General Procedure :

A mixture of **4a-h** (0.01 mol) and formamide (28.35 g, 0.63 mol) was heated under reflux for 3 h. After coollng, the precipitated product was filtered off and washed several times with cold water and recrystallized from dioxane.

3-Methyl-6(*H*) -5-oxo - 4-spiropyrazolo[4',5':5,6]pyrano[2,3-*d*]pyrimidines (**7a-h**)

General Procedure:

A mixture of **4a-h** (0.01 mol) and formic acid (6.10 g, 0.13 mol) in formamide (22.68 g, 0.50 mol) was refluxed for 5 h. After cooling, the reaction mixture was poured into an ice/water mixture and the solid product thus formed was filtered off and recrystallized from dioxane.

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