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SYNTHESIS OF NEW PYRAZOLES FROM CHALCONES

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Condensation of chalcones (**1-3**) with *p*-sulfamylphenylhydrazine hydrochloride in presence of sodium acetate afforded the corresponding hydrazones (**13-15**). Subsequent boiling of the hydrazones (**13-15**) in ethanol containing few drops of hydrochloric acid gave the corresponding pyrazolines (**7-9**). Oxidation of the pyrazolines (**7-9**) with aq bromine furnished 3,5-disubstituted pyrazoles (**16-18**). When pyrazolines (**10-12**) were treated with bromine in chloroform, they underwent oxidative bromination giving the dibromopyrazoles (**19-21**).

There is a considerable interest in the chemotherapeutic activity of pyrazole derivatives. This includes analgesics[1], antibacterials[2,3] antiflammatory[4,5] and hypoglycemic[6-8] activities. Chalcones have been extensively used to synthesize pyrazoles[9-12]. In the present study, we uses this strategy for the synthesis of new pyrazole derivatives in the hope that they may possess antimicrobial activity.

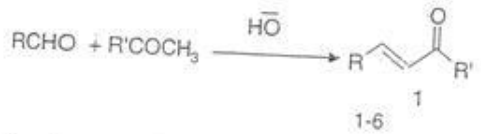
The chalcones (**1-6**) were prepared from the reaction of heterocyclic aldehydes with different substituted ketones, in presence of dil sodium hydroxide in the molar ratio (1:1:1).

The infrared spectra of the prepared chalcones (**1-6**) showed a carbonyl absorption in the region 1655-1665 cm^{-1} which is characteristic of the α,β–unsaturated carbonyl group as well as an olefinic C=C band in the region 1604-1611. The electronic spectra exhibited two absorption maxima in the regions 234-270 nm and 294-320 nm.

The ^1H NMR spectra showed the olefinic protons H-β- and H-α as two doublets (J=16Hz) in the regions at δ 6.5-6.72 and 7.42-7.68 ppm respectively. The aromatic protons appeared as multiplets at 6.52-8.05 ppm region (Table-1).

On the other hand, reaction of *p*-sulfamylphenylhydrazine hydrochloride with chalcones (**1-3**) in the presence of sodium acetate yielded the corresponding hydrazones (**13-15**) which were easily cyclized to the pyrazoline derivatives (**7-9**), when their solution in ethanol was boiled with few drops of conc. HCl (Scheme-1).

The IR spectra of hydrazones (**7-9**) showed two strong



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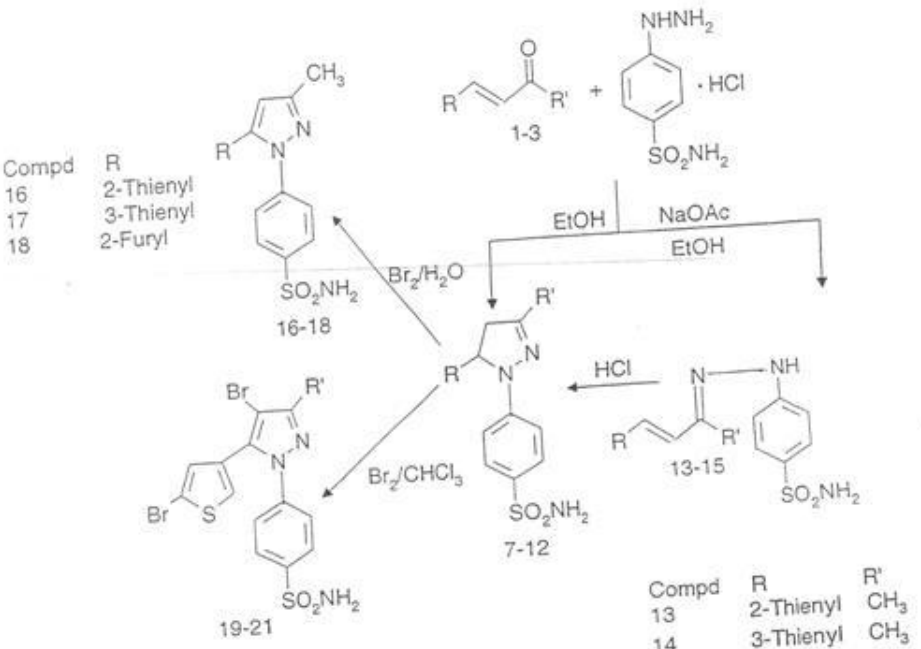
1-6

Compd	R	R'	Compd	R	R'
1	2-Thienyl	CH_3	4	3-Thienyl	C_6H_5
2	3-Thienyl	CH_3	5	3-Thienyl	*p*-BrC_6H_4
3	2-Furyl	CH_3	6	3-Thienyl	*p*-$CH_3C_6H_4$



Compd	R
16	2-Thienyl
17	3-Thienyl
18	2-Furyl

Compd	R	R'
13	2-Thienyl	CH_3
14	3-Thienyl	CH_3
15	2-Furyl	CH_3

Compd	R'
19	C_6H_5
20	*p*-BrC_6H_4
21	*p*-$CH_3C_6H_4$

SCHEME-1

absorptions at 1600-1610 and 1620-1632 for C=C and C=N respectively, as well as two bands at 1335-1350 and 1170-1185 due to the SO_2N group. The NH and NH_2 functions appeared in the regions 3150-3250 and 3350-3372.

On the other hand, the IR spectra of the pyrazoline derivatives (**7-12**) displayed two absorption bands at 3250-3264 and 3370-3380 indicative of the NH_2 group, a band at 1615-1625 for the C=N in addition to two strong bands at 1330-1355 and 1170-1185 for the SO_2N group. The structure of the pyrazolines (**7-12**) was further confirmed form their ^1H NMR spectra which exhibited besides the aromatic protons, two multiplets at 5.50-5.73 and 2.62-4.08 ppm. The low field multiplet is assigned to H-5 of the pyrazoline while the other multiplet to H-4 (Table-2). The ^1H NMR spectra of the hydrazone derivatives (**13-15**) exhibited an exchangeable NH broad singlet at 9.28-9.60, as well as the aromatic protons at 6.66-7.95 ppm (Table-1).

Mild oxidation of the pyrazoline derivatives (**7-9**) with bromine water afforded the corresponding 3,5-disubstituted pyrazoles (**16-18**) in low yield (20-25%) since the oxidation was always accompanied by the formation of a gummy material from which no solid could be separated. However, we tried to use other oxidizing reagents such as H_2O_2/AcOH and *p*-chloranil but no

Table-1
^{1}H NMR spectral data (δ/ppm)[a] of chalcones and hydrazones

Compd	R	R'	Olefinic	H	ArH or ArH and NH_2 (m)	Others
			H-α (d, J=16Hz)	H-β (d, J=16Hz)		
1	2-Thienyl	CH_3	7.68	6.5	7.00-7.50 (3H)	2.38(s, 3H, CH_3)
2	3-Thienyl	CH_3	b	6.72	7.50-8.05 (5H)	2.30 (s, 3H, CH_3)
3	2-Furyl	CH_3	7.42	b	6.52-6.8 (3H)	2.34 (s, 3H, CH_3), 7.55 (d, 1H, H-5 Furyl)
4	3-Thienyl	C_6H_5	b	b	6.95-7.92 (10H)	
5	3-Thienyl	p-BrC_6H_4	b	b	7.05-7.85 (9H)	
6	3-Thienyl	p-$CH_3C_6H_4$	b	b	7.20-8.00 (9H)	2.42 (s, 3H, CH_3)
13	2-Thienyl	CH_3	7.85	b	6.88-7.85 (8H)	2.18 (s, 3H, CH_3), 6.65 (s, 2H, NH_2), 9.3 (s, 1H, NH)
14	3-Thienyl	CH_3	b	b	6.86-7.90 (9H)	2.15 (s, 3H, CH_3), 6.70 (s, 2H, NH_2), 9.28 (s, 1H, NH)
15	2-Furyl	CH_3	b	b	6.50-7.55 (10H)	2.10 (s, 3H, CH_3), 7.78 (d, 1H, H-5) furly, 9.60 (s, 1H, NH)

a: Solutions in mixture of $CDCl_3$ and DMSO-d_6.

b: Overlapped by the aromatic multiplets.

satisfactory results were obtained.

On the other hand, mild oxidation of the pyrazoline derivatives (**10-12**) with bromine/water or hydrogen peroxide in acetic acid always gave starting materials unchanged.

Bromination of pyrazolines (**10-12**) with bromine in chloroform afforded the corresponding dibromopyrazoles (**19-21**).

The first step in this reaction may be the oxidation of the pyrazoline derivatives to the corresponding pyrazole followed by bromination of the pyrazoline ring as well as the active heterocyclic moiety in position-5.

However, bromination of pyrazoline derivatives (**7-9**) gave only a gummy material. This may be due to the oxidation of the CH_3 group in position-3 partially or completely with bromine, accompanied by multi bromination of the compounds. The ^{1}H NMR spectral data of the pyrazole derivatives (**16-21**), (Table-2), in agreement with the suggested structures, exhibited the aromatic and the NH_2 protons in the region 6.85-8.26 and lacked the two signals characteristic of H-4 and H-5 of the corresponding pyrazolines. It is worthy to mention that in the ^{1}H NMR spectra of the pyrazole derivatives (**16-18**), generally no separate signals could be assigned for H-4 protons of the pyrazole ring. These protons usually resonate in the same region as the complex multiplet of the side chain aromatic protons.

Experimental

^{1}H NMR spectra were recorded on a Bruker DPX-400 FT-NMR or on a 390-90 MHz spectrometer. IR spectra were recorded on a Nicolet FT-IR Spectrometer Magna 520 and Microanalyses were performed on a 2400 Perkin Elmer Series 2 CHNS Analyser.

Table-2
^{1}H NMR spectral data (δ/ppm)[a] of pyrazoline and pyrazole derivatives

Compd	R	R'	Pyrazoline H-α (2H, m)	H's H-β (q, 1H, J=6Hz)	ArH and NH_2(m)	Others
7	2-Thienyl	CH_3	2.65	5.68	6.85-7.70 (9H)	2.02 (s, 3H, CH_3)
8	3-Thienyl	CH_3	3.72	5.34	6.90-7.85 (9H)	2.12 (s, 3H, CH_3)
9	2-Furyl	CH_3	2.62-3.70	5.5	6.4 (s, H-3 Furan) 6.88-7.80 (6H)	2.10 (s, 3H, CH_3)
10	3-Thienyl	C_6H_5	2.80	5.63	6.90-7.96 (14H)	
11	3-Thienyl	p-BrC_6H_4	3.71	5.73	6.95-7.85 (11H)	and 6.70 (s, 2H, NH_2)
12	3-Thienyl	p-$CH_3C_6H_4$	-	5.55	6.90-7.74 (13H)	1.10 (s, 3H, CH_3)
16	2-Thienyl	CH_3	3.02-		6.85-8.15 (10H)	2.32 (s, 3H, CH_3)
17	3-Thienyl	CH_3	4.02		6.88-8.20 (10H)	2.30 (s, 3H, CH_3)
18	2-Thienyl	CH_3	3.25-		6.60-7.85 (10H)	2.26 (s, 3H, CH_3)
19	3-Thienyl	C_6H_5	4.08		7.00-8.24 (13H)	
20	3-Thienyl	p-BrC_6H_4	3.05		7.05-8.26 (12H)	
21	3-Thienyl	p-$CH_3C_6H_4$	4.01		7.00-8.22 (12H)	2.43 (s, 3H, CH_3)

a. Solutions in mixture of $CDCl_3$ and DMSO-d_6.

General method for preparation of chalcones (1-6)

A solution of NaOH (0.05 mol) in water (25 ml) and ethanol (15 ml) was stirred and cooled. To this solution heterocyclic aldehyde (0.05 mol) was added followed by the appropriate ketone (0.05 mol). The temp of the mixture was kept at 25-30° and stirring was continued for 3 hr, After keeping the reaction mixture in the refrigerator overnight, the chalcones that separated out were collected (88-94%) and identified. (Table-1).

Preparation of Heterocyclic hydrazones (13-15)

A solution of the appropriate chalcone (1, 0.01 mol) in ethanol (30 ml) was refluxed with a mixture of *p*-sulfamylphenylhydrazine hydrochloride (0.011 mol) and sodium acetate (0.011 mol) in water (3 ml) for one hr and poured into ice-cold water. The precipitated product was filtered and recrystallized from ethanol in needles (75-85% yield). (Tables 1 and 3).

Preparation of pyrazoline derivatives (7-12)

A solution of the appropriate chalcone (1, 0.01 mol) in ethanol (30 ml) was refluxed with *p*-sulfamylphenylhydrazine hydrochloride (0.01 mol) for 2 hr concentrated and cooled. The precipitated crude product was collected and recrystallized from ethanol (85-88% yield) (Tables 2 and 3).

The pyrazolines **6,8** and **9** were also prepared by refluxing the appropriate hydrazone (0.01 mol) in ethanol (20 ml) with 35% HCl (0.5 ml) for 1 hr. The reaction mixture was then concentrated and the precipitated products were crystallized from ethanol to give the corresponding pyrazolines **7-9** as pale yellow crystals (80-85% yield).

Table-3
Characterization data of hydrazones, pyrazolines and pyrazole derivatives

Compd	R	R'	M.P. (°C)	Mol formula	Found (Calcd) C	H	N	S
7	2-Thienyl	CH_3	130	$C_{14}H_{15}N_3O_2S_2$	52.26(52.34)	4.74(4.67)	12.93(13.08)	19.82(19.93)
8	3-Thienyl	CH_3	150	$C_{14}H_{15}N_3O_2S_2$	52.42(52.34)	4.51(4.67)	13.04(13.08)	20.10(19.93)
9	2-Furyl	CH_3	164	$C_{14}H_{15}N_3O_2S$	55.30(55.08)	4.78(4.92)	13.48(13.77)	10.52(10.49)
10	3-Thienyl	C_6H_5	220	$C_{19}H_{17}N_3O_2S_2$	59.40(59.53)	4.80(4.43)	10.71(10.96)	16.41(16.71)
11	3-Thienyl	p-BrC_6H_4	194	$C_{19}H_{16}BrN_3O_2S_2$	49.60(49.35)	3.63(3.46)	8.70(9.09)	13.70(13.85)
12	3-Thienyl	p-$CH_3C_6H_4$	216	$C_{20}H_{19}N_3O_2S_2$	60.51(60.45)	5.00(4.78)	10.61(10.57)	16.20(16.12)
13	2-Thienyl	CH_3	177	$C_{14}H_{15}N_3O_2S_2$	52.50(52.34)	5.00(4.67)	13.20(13.08)	19.80(19.93)
14	3-Thienyl	CH_3	160	$C_{14}H_{15}N_3O_2S_2$	52.10(52.34)	4.68(4.67)	13.13(13.08)	20.20(19.93)
15	2-Furyl	CH_3	205	$C_{14}H_{15}N_3O_3S$	54.91(55.08)	5.00(4.92)	13.56(13.77)	10.62(10.49)
16	2-Thienyl	CH_3	152	$C_{14}H_{12}N_3O_2S_2$	52.32(52.66)	3.92(4.07)	13.38(13.16)	19.90(20.06)
17	3-Thienyl	CH_3	183	$C_{14}H_{13}N_3O_2S_2$	52.25(52.66)	3.80(4.07)	12.82(13.16)	19.81(20.06)
18	2-Furyl	CH_3	172	$C_{14}H_{13}N_3O_3S$	55.62(55.44)	3.99(4.29)	13.78(13.86)	10.30(10.56)
19	3-Thienyl	C_6H_5	194	$C_{19}H_{13}Br_2N_3O_2S_2$	42.10(42.30)	2.60(2.40)	8.10(7.79)	11.70(11.87)
20	3-Thienyl	p-BrC_6H_4	178	$C_{19}H_{12}Br_3N_3O_2S_2$	36.60(36.89)	2.20(1.94)	7.00(6.79)	10.50(10.35)
21	3-Thienyl	p-$CH_3C_6H_4$	222	$C_{19}H_{15}Br_2N_3O_2S_2$	43.10(43.39)	2.50(2.71)	7.80(7.59)	11.80(11.57)

3,5-Disubstituted 1-(*p*-sulfamylphenyl) pyrazoles (16-18)

A suspension of the appropriate pyrazoline (**7-9**, 0.01 mol) in water (10 ml) was treated with 10% bromine water with stirring until faint yellow colour developed. The stirring was continued overnight, and the crude product filtered and recrystallized from methanol as needles (20-25%) (Tables 2 and 3). The mother liquor on concentration afforded a gummy material from which no solid could be isolated. The pyrazolines (**10-12**) were recovered unchanged, when treated with bromine/water under the above condition.

Bromination of pyrazoline derivatives

A solution of the appropriate pyrazoline derivative (**10-12**, 0.01 mol) in chloroform (15 ml) was stirred with a solution of bromine (0.02 mol) in chloroform (5 ml) for 1 hr. The solvent was then removed under reduced pressure and the solid residue which remained was recrystallized from methanol to give the dibromopyrazoles (**19-21**, 65-72%) as needles. (Tables 2 and 3). Bromination of the pyrazoline derivatives (**7-9**) under the same condition gave only a gummy material from which no solid could be obtained.

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