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SYNTHESIS OF NEW PYRAZOLINE AND PYRAZOLE DERIVATIVES

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Condensation of *p*-sulfamylphenylhydrazine with chalcones, leads either to hydrazones (**2**) or pyrazolines (**3**). Oxidation of (**3**) afforded pyrazole derivatives (**4**). Benzenesulfonylureas (**5**) and thioureas (**6**) were also prepared, and (**6**) was converted to the corresponding thiazolidinones (**7**) on reaction with ethyl bromoacetate.

A wide variety of pharmacological properties have been associated with di-and trisubstituted pyrazoles including antiinflammatory[1], antibacterial[2], antineoplastic[3] antiallergic[4] and hypoglycemic activities[5]. In this report some new trisubstituted pyrazoles were prepared as possible hypoglycemic agents.

Condensation of the key intermediate, *p*-sulfamylphenylhydrazine hydrochloride with substituted chalcones (**1**) afforded 3,5-diaryl-l-(*p*-sulfamylphenyl)-Δ^2-pyrazolines **3**. However, reaction of *p*-sulfamylphenylhydrazine hydrochloride with chalcones (**1**) in the presence of sodium acetate and a few drops of acetic acid yielded the corresponding arylhydrazones (**2**) which were easily cyclized to pyrazolines (**3**) when boiled with few drops of HCl. The IR spectrum of (**2**A) showed two strong absorption bands at 1600-1610 and 1620-1645 cm^{-1} for C=C and C=N respectively, as well as two bands at 1335-1350 and 1170-1185 due to the $SO_2N<$ function. The NH appeared in 3150-3250 region. On the other hand IR spectra of the pyrazoline derivatives (**3**) displayed two absorption bands at 3250-3264 and 3370-3385 indicative of the NH_2 group, a band at 1615-1625 for C=N in addition to two strong bands at 1330-1355 and 1170-1185 for the $SO_2N<$ group. The structure of pyrazolines (**3**) was further confirmed from their ^1H NMR spectra which exhibited besides the aromatic signals, two multiplets at δ 5.3-5.6 and 2.9-4.2. The low field multiplet is assigned to H-5 of the pyrazoline while the other multiplet to H-4 (Table-2).

Mild oxidation of the pyrazoline derivatives (**3**) with bromine water led to the formation of the corresponding pyrazoles (**4**). In consistant with the proposed structures the ^1H NMR spectra of these pyrazoles showed the aromatic protons as multiplets in the region 6.7-8.1 and lacked the two multiplets existing in pyrazolines (**3**) Scheme-1.

Condensation of pyrazolines (**3**) with the appropriate isocyanate and isothiocyanate in presence of K_2CO_3 in dry acetone yielded the corresponding benzenesulfonylurea (**5**) and thiourea (**6**) derivatives respectively. IR spectra of these compounds exhibited two bands 1310-1366 and 1160-1180 due to $SO_2N<$ group as well as a urea carbonyl band at 1650-1670 in the case of compound (**6**). The structure of compounds (**5**) and (**6**) were further supported by their elemental analysis as well as ^1H NMR spectra.

Cyclization of the thiourea derivatives (**6**), with ethyl bromoacetate afforded the corresponding thiazolidine derivatives (**7**). In addition to the two band of the-$SO_2N<$ group at 1330-1350 and 1155-1165 the IR spectra of compounds (**7**) revealed a carbonyl absorption at 1700-1710.

Experimental

Melting points were determined on a Kofler hot stage apparatus and were uncorrected. ^1H NMR Spectra were recorded on a Varian EM 390-90 MHz spectrometer using TMS as internal standard. IR spectra were recorded on unicam SP 1025 infrared spectrometer.

Arylhydrazone derivative (2A)

A solution of appropriate chalcone (**1**; 0.01 mol) in ethanol (30 ml) was refluxed with a mixture of *p*-sulfamylphenylhydrazine hydrochloride (0.011 mol), a few drops of acetic acid and sodium acetate (0.02 mol) in water (5 ml) for 1 hr, and poured into water. The precipitated product was filtered and recrystallized from methanol to give **2A**.

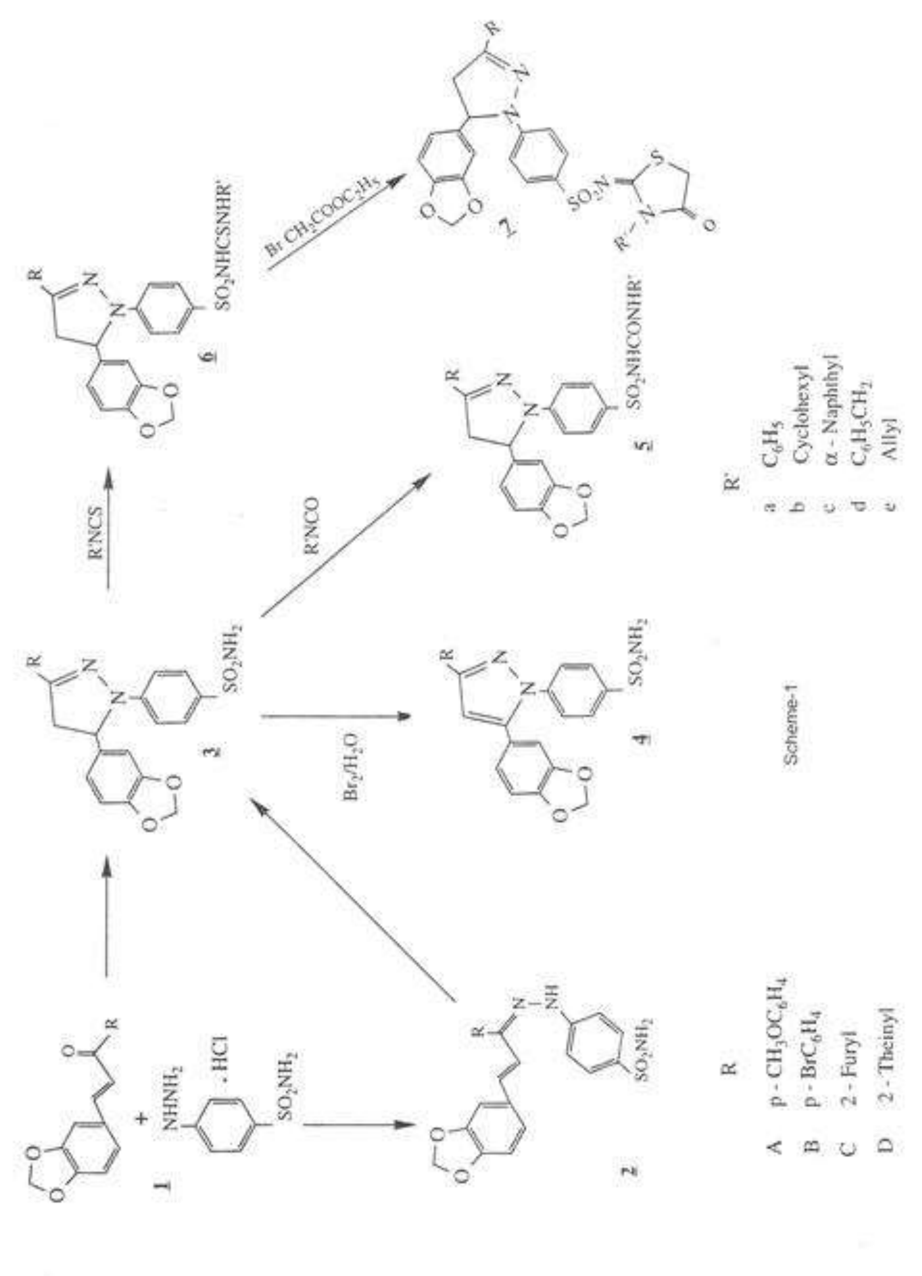
3, 5-Disubstituted 1-(*p*-sulfamylphenyl)-Δ^2-pyrazolines (3; Table-1)

A solution of appropriate chalcone (**1**; 0.01 mol) in ethanol (50 ml) was refluxed with *p*-sulfamylphenylhydrazine hydrochloride (0.011 mol) for 4 hr, cooled and diluted with water. The precipitated crude product was filtered and recystallized from ethanol as needles.

The pyrazoline **3A** was also prepared in 65% yields when a solution of **2A** (0.01 mol) in ethanol (30 ml) was refluxed with HCl (0.5 ml) for 2 hr.

3,5-Disubstituted 1-(*p*-sulfamylphenyl) pyrazoles (4; Table-1)

A suspension of **3** (0.01 mol) in water (10 ml) was


1
2
3
4
5
6
7
R'NCS
R'NCO
Br$_2$/H$_2$O
Br CH$_2$COOC$_2$H$_5$
SO$_2$NH$_2$
SO$_2$NHCSNHR'
SO$_2$NHCONHR'
R
A p - CH$_3$OC$_6$H$_4$
B p - BrC$_6$H$_4$
C 2 - Furyl
D 2 - Theinyl
R'
a C$_6$H$_5$
b Cyclohexyl
c α - Naphthyl
d C$_6$H$_5$CH$_2$
e Allyl

Scheme-1

Table-1

Characteristic data of compounds (2-7)

Compd	Yield (%)	M.P. (°C)	Mol formula	Found C	Found H	Found N	(Calcd) C	(Calcd) H	(Calcd) N
2A	69	152	$C_{21}H_{21}N_3O_5S$	60.8	4.8	9.3	61.2	4.7	9.3
3A	70	168	$C_{23}H_{21}N_3O_5S$	60.9	4.6	9.1	61.2	4.7	9.3
3B	66	184	$C_{22}H_{18}BrN_3O_4S$	52.9	3.7	8.2	52.8	3.6	8.4
3C	78	115	$C_{20}H_{17}N_3O_5S$	58.2	4.2	10.0	58.4	4.1	10.2
3D	82	190	$C_{20}H_{17}N_3O_4S_2$	56.4	3.9	9.6	56.2	4.0	9.8
4A	90	265	$C_{23}H_{19}N_3O_5S$	61.1	4.4	9.3	61.5	4.3	9.4
4C	81	195	$C_{20}H_{15}N_3O_5S$	58.8	4.2	10.1	58.7	3.7	10.3
5Aa	78	182	$C_{30}H_{26}N_4O_6S$	63.4	4.6	9.9	63.3	4.6	9.8
5Ab	69	197	$C_{30}H_{32}N_4O_6S$	62.2	5.5	9.4	62.5	5.6	9.7
5Ac	75	220	$C_{34}H_{26}N_4O_6S$	65.6	4.5	9.0	65.8	4.6	9.0
5Ba	86	200	$C_{29}H_{21}BrN_4O_5S$	56.6	3.9	8.9	56.2	3.7	9.0
5Bb	78	205	$C_{29}H_{29}BrN_4O_5S$	55.2	4.8	8.8	55.7	4.7	9.0
5Ca	78	130	$C_{27}H_{22}N_4O_6S$	60.7	4.2	10.4	61.1	4.2	10.6
5Cb	83	164	$C_{27}H_{28}N_4O_6S$	60.1	5.2	10.3	60.4	5.3	10.4
5Cc	76	150	$C_{31}H_{24}N_4O_6S$	63.8	4.4	9.5	64.1	4.2	9.7
5Da	83	208	$C_{27}H_{22}N_4O_5S_2$	59.0	4.15	9.9	59.3	4.1	10.3
5Db	76	212	$C_{27}H_{28}N_4O_5S_2$	57.8	5.7	9.8	58.7	5.1	10.1
5Dc	80	287	$C_{31}H_{24}N_4O_5S_2$	62.7	4.4	8.9	62.4	4.1	9.4
6Aa	75	130	$C_{30}H_{26}N_4O_5S_2$	61.5	4.4	9.5	61.4	4.5	9.6
6Ad	65	166	$C_{31}H_{28}N_4O_5S_2$	61.8	4.7	9.1	62.0	4.7	9.3
6Ba	72	169	$C_{29}H_{23}BrN_4O_4S_2$	54.6	3.4	8.5	54.8	3.7	8.8
6Bd	65	106	$C_{30}H_{25}BrN_4O_4S_2$	54.7	3.6	8.8	55.5	3.9	8.6
6Be	75	110	$C_{26}H_{23}BrN_4O_4S_2$	52.5	3.8	9.1	52.1	3.9	9.3
6Ca	70	154	$C_{27}H_{22}N_4O_5S_2$	58.9	3.8	9.7	59.3	4.1	10.3
6Cd	74	170	$C_{28}H_{24}N_4O_5S_2$	59.8	4.3	9.9	60.0	4.3	10.0
6Da	60	130	$C_{27}H_{22}N_4O_4S_3$	57.4	3.6	9.7	57.7	3.9	10.0
6Dd	65	135	$C_{28}H_{24}N_4O_4S_3$	57.9	4.0	9.6	58.3	4.2	9.7
6De	70	154	$C_{24}H_{22}N_4O_4S_3$	55.1	4.0	10.7	54.8	4.2	10.6
7Aa	75	103	$C_{32}H_{28}N_4O_5S_2$	61.0	4.4	8.7	61.3	4.2	8.9
7Ad	65	186	$C_{33}H_{28}N_4O_6S_2$	61.5	4.6	9.0	61.9	4.4	8.7
7Ae	70	101	$C_{29}H_{26}N_4O_6S_2$	58.7	4.8	9.6	59.0	4.4	9.5

Table-2

^{1}H NMR Spectral data of compounds^a (3-7)

Compd	H-4 (2H, m)	H-5 (1H, m)	CH_2 (2H,s)	Ar-H (m)	NH_2 OR NH (s)	Other
3A	3.6 - 5.1	5.2 -5.5	6.1	6.8 -8.0	6.7	3.8 (3H,s, OCH_3)
3B	2.9 - 3.9	5.2 - 5.6	6.0	6.8 - 7.8	6.7	
3C	3.1 - 4.1	5.2 - 5.6	6.0	6.7 - 7.8	6.5	
3D	2.9 - 4.2	5.3 - 5.6	5.9	6.6 - 7.9	6.4	
4A			6.0	6.9 - 7.0	6.7	3.9 (3H, s, OCH_3)
4B			6.0	7.0 - 7.8	6.8	
4C			5.9	6.9 - 8.1	6.8	
4D			6.1	7.0 - 8.0	6.9	
5Aa	3.2 - 3.8	5.2 - 5.6	5.9	6.8 - 8.0	8.1, 8.5	3.9 (3H, s, OCH_3)
5Ac	2.8 - 3.6	5.2 - 5.5	5.9	6.8 - 8.0	8.2, 8.4	3.9 (3H, s, OCH_3)
5Cb	3.2 - 4.1	5.3 - 5.6	5.9	6.6 - 7.8	8.2, 8.41.	3 - 1.8 (11H, m, cyclohexyl)
6Aa	3.1 - 3.9	5.2 - 5.6	6.0	6.9 - 7.9	8.1, 8.4	3.9 (3H, s, OCH_3)
7Ad	3.2 - 4.2	5.1 - 5.5	5.9	6.9 - 8.0		3.9 (3H, s, OCH_3) 4.8 (2H, s, CH_2) 4.85 (2H, s, CH_2)
7Ae^b	3.3 - 4.2	5.1 - 5.6	5.9	6.7 - 8.1		3.8 (3H, s, OCH_3) 4.85 (2H, s, CH_2)

^{a} Solutions in a mixture of $CDCl_3$ and DMSO - d_6

^{b} Allyl protons overlapped by the multiplets of H-4 and H-5

treated with 5% bromine water with stirring until a faint yellow colour developed. The stirring was continued for 2hr, and the crude pyrazole collected and recystallized from methanol as needles.

Substituted *p*-(3,5-diayl-Δ^2-pyrazolin-1yl) benzenesulfonylthioureas (6; Table-1)

A mixture of **3** (0.01 mol) and anhyd potassium carbonate (0.02 mol) in dry acetone (25 ml) was stirred and treated with the appropriate isothiocyanate (0.012 mol). After the mixture was stirred and refluxed for 10 hr, acetone was removed under reduced pressure, and the solid mass dissolved in water and acidified with 2N HCl. The crude product was purified by recrystallization from ethanol as needles.

3-Phenyl-2-[*p*-(3, 5-diaryl-Δ^2-pyrazoline-1-yl) benzenesulfonylimino]-4-oxothiazolidines (7; Table-1)

A mixture of **6** (0.01 mol) and ethyl bromoacetate (0.011 mol) in abs ethanol (50 ml) was refluxed with stirring for 2hr, concentrated and allowed to cool. The product obtained was recrystallized from ethanol as needles.

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