Pak. j sci. ind. res., vol. 35, no. 11, November 1992

TRIAZOLE-PYRAZOLE COMPOUNDS WITH POSSIBLE BIOLOGICAL ACTIVITY. *Part -II*

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(Received October 4, 1992)

Condensation of 4-formyl-2-aryl-1,2,3- triazoles with acetophenone derivatives afforded the chalcone (1) which react with different acyl- and arylhydrazines to give the corresponding hydrazones (2 and 3) or pyrazolines (4). Oxidation of (4) with bromine water yielded the pyrazole derivatives (5). Condensation of (4) and (5) with isothiocyanate gave the thioureas (6) and (7), which cyclized with ethyl bromoacetate to the corresponding thiazolidines (8) and (9).

Key words: Triazole, Chalcones, Pyrazoles.

Introduction

The fact that many pyrazoles and triazole derivatives possess substantial pharmacological [1-6] and biological [7-10] properties, led us to a study of compounds having both moieties.

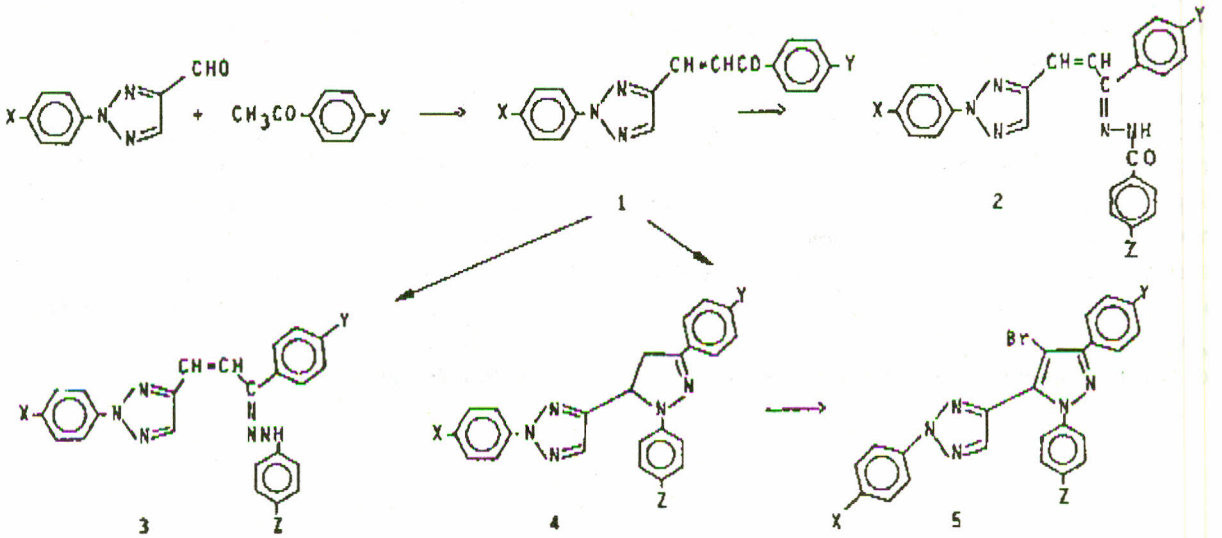
Materials and Methods

Synthesis of the compounds. 4-Formyl-2-aryl-1,2,3-triazoles prepared by the literature methods [11,13] were reacted with acetophenone and substituted acetophenones to give the corresponding α, β-unsaturated ketones (1; Table 1). The IR spectra of the above chalcones revealed a carbonyl absorption at 1655-1665 cm^{-1} as well as an olefinic C=C stretching in the 1604-1611 cm^{-1} region. The structure was further supported by their ^1H and ^{13}C nmr spectra (Tables 2 and 3).

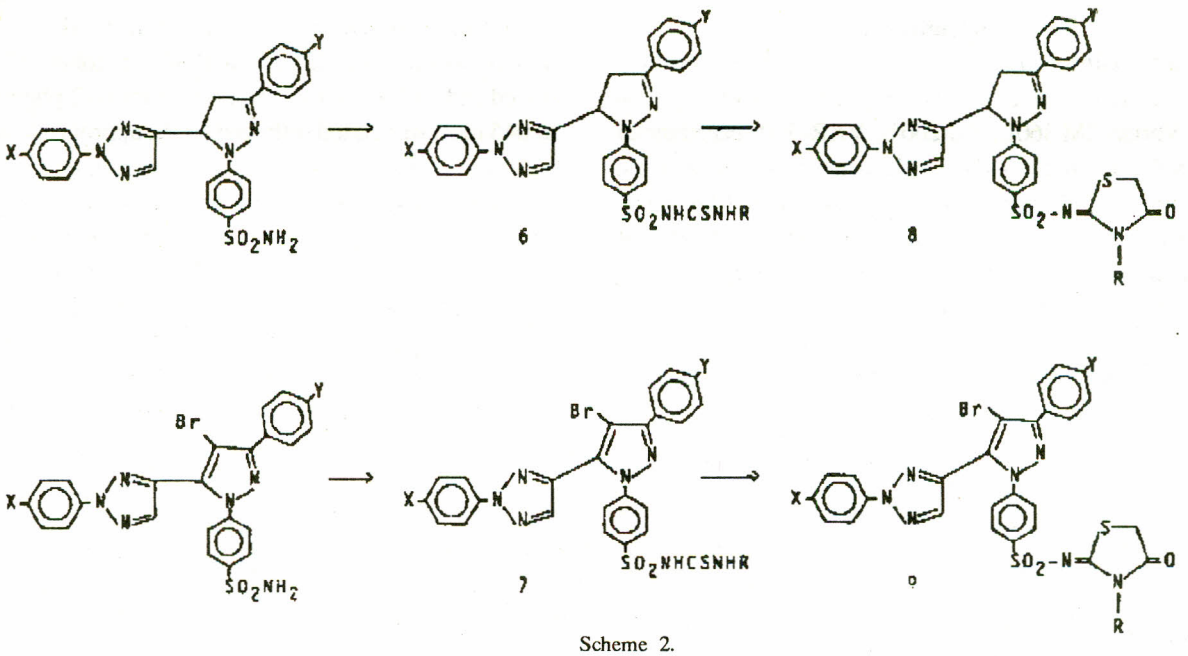
Condensation of the foregoing chalcones with appropriate acylhydrazines in presence of acid catalyst afforded the corresponding acylhydrazones (2; Table 4). Their IR spectra exhibited an amide carbonyl absorption at 1652-1660 cm^{-1}, NH at 3120-3200 cm^{-1} and C=N stretching at 1620-1631cm^{-1}.

Similarly condensation of chalcones (1) with arylhydrazines afforded the arylhydrazone derivatives (3; Table 4) which were easily cyclized to the corresponding pyrazolines (4; Table 5) when boiled with few drops of hydrochloric acid. However, the pyrazoline derivatives (4) were also obtained from the corresponding α, β-unsaturated ketone and the appropriate arylhydrazine hydrochloride. The structures of the arylhydrazone as well as the pyrazoline derivatives were supported by ^1H NMR spectra of pyrazolines (4) (Tables 2 and 3) which exhibited besides the aromatic signals at δ7.05-8.70, two multiplets at δ5.11-6.43 and 3.11-4.55 for H-4 and H-5 of the pyrazoline ring, respectively.

Oxidation of pyrazolines (4) with excess of bromine water afforded the corresponding 4-bromopyrazoles (5; Table 5). Their ^1H nmr spectra (Table 2) displayed the aromatic protons as multiplet in the δ7.32-8.70 region and lacked the two signals characteristic of H-4 and H-5 of the corresponding



Scheme 1.



Scheme 2.

TABLE 1. MICROANALYSIS OF CHALCONES (1).

Compd. No.	X	Y	Yield (%)	M.p. (°C)	Mol. formula	Found C	Found H	Found N	Calc. C	Calc. H	Calc. N
1a	Cl	H	85	155	$C_{17}H_{12}N_3OCl$	65.63	3.61	13.41	65.92	3.90	13.65
1b	Cl	Cl	80	170	$C_{17}H_{11}N_3OCl_2$	59.55	3.31	11.90	59.31	3.22	12.21
1c	Cl	Br	78	160	$C_{17}H_{11}N_3OBrCl$	52.76	2.86	11.13	52.54	2.85	10.81
1d	Cl	CH_3	75	160	$C_{18}H_{14}N_3OCl$	67.10	4.27	12.73	66.97	4.36	12.98
1e	Br	H	70	170	$C_{17}H_{12}N_3OBr$	67.58	3.66	11.87	57.64	3.41	11.86
1f	Br	Cl	65	205	$C_{17}H_{12}N_3OBrCl$	52.36	2.71	10.76	52.40	3.10	10.78
1g	Br	Br	79	178	$C_{17}H_{11}N_3OBr_2$	46.94	2.80	9.49	47.14	2.56	9.70
1h	Br	CH_3	72	205	$C_{18}H_{14}N_3OBr$	58.67	4.09	11.13	58.71	3.83	11.41

TABLE 2. ^{1}H NMR SPECTRAL DATA (δ/PPM) OF COMPOUNDS (1-5).

Compd. No.	^{1}H NMR Triazole H-5 (1H, s)	Pyrazoline H H-4 (2H,m)	Pyrazoline H H-5 (1H,m)	Olefinic and/or ArH (m)	(CH_3, s) (3H, s)	NH_2 (2H, sb)
1a	9.22			7.35-8.1(11H)		
1b	9.21			8.12-8.66(10H)		
1d	a			7.00-8.05(11H)	2.28	
1f	9.23			7.10-7.82(10H)		
1h	a			7.15-8.00(11H)	2.35	
2d	9.2			7.62-8.60(15H)b	2.38	
2g	9.18			7.50-8.55(15H)b		6.85
4a	a	3.55	5.53	7.10-8.05(14H)		
4c	9.20	4.18	6.35	7.50-8.65(13H)		
4h	a	3.6	5.56	7.50-8.00(14H)		
4i	9.19	4.19	6.30	7.60-8.70(13H)	2.65	
5b	9.20			7.85-8.92(13H)		6.90
5d	9.28			7.56-8.70(12H)		6.95
5e	9.22			7.55-8.60(14H)		
5g	a			7.32-8.15(14H)		
5i	9.18			7.65-8.66(12H)	2.55	7.00

a = Overlapped by the aromatic protons. b = NH overlapped by the aromatic protons.

pyrazolines. The ^{13}C nmr spectra of the above pyrazoles (5) (Table 3) are consistent with the assigned structures. It showed the expected number of signals for the aromatic carbon and lacked the two signals of C-4 and C-5 existing in the corresponding pyrazoline derivatives.

Reaction of pyrazoline (4) and pyrazole (5) derivatives with the appropriate isothiocyanate in dry acetone afforded the corresponding thioureas (7 and 8; Table 6) respectively. The IR spectra of these compounds revealed two bands at 1150-1165 cm^{-1} and 1338-1340 cm^{-1} due to SO_2N group as well as a C=S stretching at 1082-1100 cm^{-1}.

Cyclocondensation of the thioureas (7 and 8) with ethyl bromoacetate afforded the corresponding 4-oxothiazolidines (9 and 10) respectively (Table 6). Their IR spectra exhibited a cyclic carbonyl absorption at 1730-1747 cm^{-1} in addition to the two bands of the SO_2N group at 1152-1155 cm^{-1} and 1334-1338 cm^{-1}.

Experimental

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. ^{1}H nmr spectra were recorded on either a Varian EM 360L, XL-200 or VXR-300 spectrometer using TMS as internal standard. ^{13}C nmr spectra were recorded on the Varian XL-200 or VXR-300 spectrometer. Mass spectra were determined on a Kratos M 30 instrument. The IR spectra were measured on a Unicam SP 1025 spectrophotometer using KBr pellets. Electronic spectra were recorded on a Unicam 1805 programme controller instrument. Microanalyses were performed at the Microanalytical Unit, Faculty of Science, University of Cairo, Egypt.

Chalcone derivatives (1). A solution of sodium hydroxide (0.055 mol) in water (25 ml) and ethyl alcohol (15 ml) was stirred and cooled. To this solution 4-formyl-2-phenyltriazole (0.045 mol) was added followed by the appropriate acetophenone derivative (0.045 mol). The temperature of the mixture was kept at 25° and stirring was continued for 3 hrs. After keeping the reaction mixture in the refrigerator overnight, the solid chalcone that separated out was filtered off, washed with water and crystallised from alcohol (Table 1).

Aroylhydrazone derivatives (2). A solution of the appropriate chalcone (1; 0.01 mol) in toluene (30 ml) was refluxed with the corresponding aroylhydrazine (0.011 mol) in pres-

Table 3. ^{13}C NMR Spectral Data of Compounds (1-5).

Compd. No.	CH_3	Pyrazoline C C-3	C-4	C-5	Aryl, triazole and pyrazole C	C-α	C-β	C=O
1b					120.2,125.6,129.0, 130.4,131.3,132.5, 135.5,136.8,137.5, 145.9	138.5	129.7	187.5
1g					117.1,125.4,127.7, 128.3,130.0,131.6, 131.8,136.1,136.4, 145.6	138.7	129.5	187.8
4a		149.6	40.7	55.6	114.7,118.0,119.1, 122.7,125.7,127.5, 128.6,129.3,131.7, 134.3,136.4,138.9, 143.2,145.6			
4c		149.6	40.5	55.9	114.7,118.0,119.1, 123.1,125.2,126.9, 128.0,129.3,131.6, 134.5,136.8,138.6, 143.0,145.4			
4i	20.60	149.7	40.6	55.8	114.5,118.2,119.6, 123.4,125.5,127.6, 128.5,129.1,131.6, 134.2,136.4,138.8, 143.2,145.5			
5b					112.5*,120.1,125.6, 126.9,128.8,129.5, 130.2,131.1,132.4, 133.8,134.6,135.5, 136.6,137.6,138.3, 145.8,147.3			
5i	20.78				113.0*,121.5,125.8, 127.1,128.9,129.6, 130.4,131.5,132.4, 133.7,134.5,135.6, 136.8,137.5,138.5, 145.9,148.8.			

* Pyrazole C-4.

TABLE 4. MICROANALYSIS OF HYDRAZONES (2 AND 3).

Compd. No.	X	Y	Z	Yield (%)	M.p. (°C)	Mol. formula	Found C	Found H	Found N	Calc. C	Calc. H	Calc. N
2a	Cl	H	H	60	137	$S_{23}H_{18}N_5Cl$	69.18	4.48	17.38	69.08	4.54	17.51
2b	Cl	H	SO_2NH_3	75	175	$C_{23}H_{19}N_6O_2ClS$	57.81	3.65	17.40	57.68	4.00	17.55
2c	Cl	Cl	H	55	123	$C_{23}H_{17}N_5Cl_2$	63.95	4.09	16.09	63.60	3.94	16.12
2d	Cl	Cl	CH_3	62	180	$C_{24}H_{19}N_5Cl_2$	64.02	4.38	15.68	64.29	4.27	16.62
2e	Cl	Cl	SO_2NH_2	65	178	$C_{23}H_{18}N_6O_2Cl_2S$	53.60	3.86	16.39	53.81	3.53	16.37
2f	Cl	Br	H	69	127	$C_{23}H_{17}N_5BrCl$	57.36	3.50	14.26	57.70	3.58	14.63
2g	Cl	Br	SO_2NH_2	70	170	$C_{23}H_{18}N_6O_2BrClS$	49.30	3.16	15.42	49.52	3.25	15.06
2h	Br	H	H	68	154	$C_{23}H_{18}N_5Br$	62.36	4.37	15.42	62.17	4.08	15.76
2i	Br	H	SO_2NH_2	72	180	$C_{23}H_{19}N_6O_2BrS$	52.95	3.66	15.99	52.78	3.66	16.06
2j	Br	Br	CH_3	67	185	$C_{24}H_{19}N_5OBr_2$	53.29	3.80	12.80	53.65	3.65	13.04
2k	Br	Br	SO_2NH_2	73	185	$C_{23}H_{18}N_6O_2Br_2S$	45.54	3.22	13.91	45.86	3.01	13.95
2i	Br	CH_3	SO_2NH_2	66	192	$C_{24}H_{21}N_6O_2BrS$	53.85	3.97	16.01	53.64	3.94	15.94
3a	Cl	H	H	65	163	$C_{24}H_{18}N_5OCl$	67.60	4.53	16.50	67.37	4.24	16.37
3b	Cl	H	CH_3	70	142	$C_{25}H_{20}N_5OCl$	68.33	4.74	16.02	67.95	4.56	15.85
3c	Cl	Cl	H	60	139	$C_{24}H_{17}N_5OCl_2$	62.39	4.08	14.93	62.35	3.71	15.15
3d	Br	H	H	68	135	$C_{24}H_{18}N_5OBr$	61.34	3.58	14.66	61.03	3.84	14.83
3e	Br	Br	H	61	157	$C_{24}H_{17}N_5OBr_2$	52.69	2.99	13.04	52.29	3.11	12.70
3f	Br	CH_3	H	58	185	$C_{25}H_{20}N_5OBr$	61.78	4.37	14.02	61.74	4.14	14.40

TABLE 5. MICROANALYSIS OF PYRAZOLINES (4) AND PYRAZOLES (5).

Compd. No.	X	Y	Z	Yield (%)	M.p. (°C)	Mol. formula	Found C	Found H	Found N	Calc. C	Calc. H	Calc. N
4a	Cl	H	H	80	155	$C_{23}H_{18}N_5OCl$	68.88	4.50	17.14	69.08	4.54	17.51
4b	Cl	H	SO_2NH_2	89	169	$C_{23}H_{19}N_6O_2ClS$	57.66	4.09	17.23	57.68	4.00	17.55
4c	Cl	Cl	H	66	175	$C_{23}H_{17}N_5OCl_2$	63.21	3.56	16.45	63.60	3.94	16.12
4d	Cl	Cl	CH_3	65	192	$C_{24}H_{19}N_5OCl_2$	63.92	4.05	15.71	64.29	4.27	15.62
4e	Cl	Cl	SO_2NH_2	85	185	$C_{23}H_{18}N_6O_2Cl_2S$	53.76	3.23	16.58	53.81	3.53	16.37
4f	Br	H	H	72	158	$C_{23}H_{18}N_5Br$	61.98	4.45	16.10	62.17	4.08	15.76
4g	Br	H	SO_2NH_2	80	156	$C_{23}H_{19}N_6O_2BrS$	52.49	3.76	16.22	52.78	3.66	16.06
4h	Br	Br	H	75	152	$C_{23}H_{17}N_5Br_2$	53.14	3.54	13.75	52.80	3.27	13.38
4i	Br	Br	CH_3	68	160	$C_{24}H_{19}N_5Br_2$	53.46	3.51	13.31	53.65	3.56	13.04
4j	Br	Br	SO_2NH_2	66	165	$C_{23}H_{18}N_6O_2Br_2S$	45.98	2.73	13.77	45.86	3.01	13.95
4k	Br	CH_3	SO_2NH_2	76	164	$C_{24}H_{21}N_6O_2BrS$	53.49	3.84	15.40	53.64	3.94	15.64
5a	Cl	H	H	69	103	$C_{23}H_{15}N_5BrCl$	57.83	3.44	14.43	57.94	3.17	14.69
5b	Cl	H	SO_2NH_2	78	157	$C_{23}H_{16}N_6BrClS$	49.60	2.89	14.88	49.70	2.90	15.12
5c	Cl	Cl	H	60	152	$C_{23}H_{14}N_5BrCl_2$	54.36	3.10	13.52	54.04	1.76	13.70
5d	Cl	Cl	SO_2NH_2	75	172	$C_{23}H_{15}N_6O_2BrCl_2S$	47.01	2.56	13.97	46.80	2.56	14.24
5e	Br	H	H	62	165	$C_{23}H_{15}N_5Br_2$	53.19	3.20	13.84	53.00	2.90	13.49
5f	Br	H	SO_2NH_2	70	140	$C_{23}H_{16}N_6O_2Br_2S$	45.62	2.65	13.83	46.02	2.69	14.00
5g	Br	Br	H	62	142	$C_{23}H_{14}N_5Br_3$	46.08	2.75	11.40	46.03	2.35	11.67
5h	Br	Br	SO_2NH_2	65	170	$C_{23}H_{15}N_6O_2Br_3S$	40.97	2.15	12.38	40.67	2.23	12.37
5i	Br	CH_3	SO_2NH_2	78	150	$C_{24}H_{18}N_6O_2Br_2S$	46.56	2.80	13.44	46.92	2.95	13.68

ence of a few drops of glacial acetic acid for 1 hr. Toluene was removed under reduced pressure and the residue was treated with methanol to give the product which was recrystallised from benzene-methanol mixture (Table 1).

Arylhydrazone derivatives (3). A solution of (1; 0.01 mol) in ethanol (30 ml) was refluxed with a mixture of the appropriate arylhydrazine hydrochloride (0.011 mol) and sodium acetate (0.012 mol) in water (5 ml) for 1 hr. The reaction mixture was poured into water, the precipitated product was filtered off and recrystallised from alcohol (Table 1).

1,3,5-Trisubstituted-2-pyrazolines (4). A solution of the appropriate chalcone (1; 0.01 mol) in ethanol (50 ml) was refluxed with the proper arylhydrazine hydrochloride (0.011 mol) for 4 hr. cooled and diluted with water. The precipitated crude product was filtered off and recrystallised from ethanol in the form of needles (Table 1).

The pyrazolines 4 were also obtained (65% yield) by refluxing the appropriate hydrazone in ethanol with hydrochloric acid for 3hrs.

4-Bromo-1,3,5-trisubstituted pyrazoles (5). A suspension of 4 (0.01 mol) in water (10 ml) was treated with excess 5% bromine water with stirring until a faint yellow colour was developed. After stirring for 4 hr. the crude pyrazole was filtered off and recrystallised from methanol as needles (Table 1).

Substituted p-(3,5-diaryl-2-pyrazolin-1-yl)(6)-and p-(3,5-diarylpyrazol-1-yl)(7)-benzenesulfonylthioureas. A mixture of 4 or 5 (0.01 mol) and anhydrous potassium carbonate (0.02 mol) in dry acetone (25 ml) was stirred and refluxed for 1 hr. At this temperature, a solution of the appropriate isothiocyanate (0.015 mol) in dry acetone (5 ml) was added dropwise. After the mixture was stirred and refluxed for 10 hr. acetone was removed under reduced pressure, the solid mass dissolved in water and acidified with 2N HCl. Recrystallisation of the precipitate from methanol gave needles of pure product (Table 3).

3-Substituted 2-[p-(3,5-diaryl-2-pyrazolin-1-yl) benzene-sulfonylimino](8)-and 2-[p-(3,5-diarylpyrazol-1-yl)benzene- sulfonylimino] (9)-4-oxothiazolidines. A mixture of 6 or 7 (0.01 mol) and ethyl bromoacetate (0.011 mol) in

Table 6. Microanalysis of Compounds (6-9).

Compd. No.	X	Y	R	Yield %	M.p. °C	Mol. formula	Found C	Found H	Found N	Calc. C	Calc. H	Calc. N
6a	Cl	H	allyl	65	120	$C_{27}H_{24}N_7O_2ClS_2$	56.07	3.83	16.63	56.10	4.18	16.96
6b	Cl	H	*n*-C_4H_9	70	137	$C_{28}H_{28}N_7O_2ClS_2$	56.52	4.94	16.80	56.60	4.75	16.50
6d	Cl	H	C_6H_5	72	127	$C_{30}H_{24}N_7O_2ClS_2$	59.89	4.17	16.27	58.67	3.94	15.96
6e	Cl	H	C_6H_5-CH_2	68	137	$C_{31}H_{26}N_7O_2ClS_2$	58.91	4.44	15.87	59.27	4.17	15.61
6f	Cl	Cl	C_6H_5	75	117	$C_{30}H_{23}N_7O_2Cl_2S_2$	55.74	3.69	14.89	55.56	3.57	15.12
6g	Cl	Cl	C_6H_5-CH_2	62	140	$C_{31}H_{25}N_7O_2Cl_2S_2$	55.97	3.85	14.98	56.19	3.80	14.80
6h	Br	H	*n*-C_4H_9	73	147	$C_{28}H_{28}N_7O_2BrS_2$	52.92	4.28	15.75	52.66	4.42	15.35
6i	Br	H	C_6H_5	76	135	$C_{30}H_{24}N_7O_2BrS_2$	54.55	3.33	14.57	54.71	3.67	14.89
6j	Br	H	C_6H_5-CH_2	62	130	$C_{31}H_{26}N_7O_2BrS_2$	55.64	4.10	14.32	55.36	3.90	14.58
6k	Br	CH_3	C_6H_5	60	143	$C_{31}H_{26}N_7O_2BrS_2$	55.59	4.17	14.22	55.36	3.90	14.58
7a	Cl	H	C_6H_5	67	119	$C_{31}H_{21}N_7O_2BrClS_2$	51.92	3.20	14.09	52.14	3.06	14.19
7b	Cl	H	C_6H_5-CH_2	58	125	$C_{31}H_{23}N_7O_2BrClS_2$	52.54	3.38	14.11	52.81	3.29	13.91
7c	Cl	Cl	C_6H_5	78	137	$C_{30}H_{20}N_7O_2BrCl_2S_2$	49.79	2.53	13.82	49.67	2.78	13.51
7d	Cl	Cl	C_6H_5-CH_2	80	134	$C_{31}H_{22}N_7O_2BrCl_2S_2$	50.70	3.30	13.33	50.35	3.00	13.26
7e	Br	H	C_6H_5	64	152	$C_{30}H_{21}N_7O_2Br_2S_2$	49.20	2.69	13.56	48.99	2.88	13.33
7f	Br	H	C_6H_5-CH_2	73	163	$C_{31}H_{23}N_7O_2Br_2S_2$	49.79	3.17	13.27	49.68	3.09	13.08
8a	Cl	Cl	allyl	72	135	$C_{29}H_{23}N_7O_3Cl_2S_2$	53.51	3.91	14.72	53.38	3.55	15.02
8b	Cl	Cl	C_6H_5	69	105	$C_{32}H_{23}N_7O_3Cl_2S_2$	56.11	3.46	14.02	55.82	3.37	14.24
8c	Br	H	C_6H_5	70	125	$C_{32}H_{24}N_7O_3BrS_2$	55.31	4.37	14.30	55.02	3.64	14.03
9a	Cl	H	C_6H_5	68	85	$C_{32}H_{24}N_7O_3ClS_2$	59.00	3.92	14.83	58.75	3.70	14.99
9b	Cl	Cl	C_6H_5	62	100	$C_{32}H_{20}N_7O_3BrCl_2S_2$	44.88	2.57	13.83	50.21	2.63	12.81
9c	Cl	Cl	C_6H_5-CH_2	59	78	$C_{33}H_{22}N_7O_3BrCl_2S_2$	51.05	3.17	12.20	50.85	2.84	12.58
9d	Br	H	C_6H_5	63	150	$C_{32}H_{21}N_7O_3Br_2S_2$	49.57	2.67	13.34	49.56	2.73	12.64
9e	Br	H	C_6H_5-CH_2	67	155	$C_{33}H_{23}N_7O_2Br_2S_2$	49.94	2.79	12.79	50.20	2.94	12.42

absolute ethanol (50 ml) was refluxed with stirring for 6 hrs. concentrated and allowed to cool. The product obtained was recrystallised from ethanol in the form of needles (Table3).

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