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SYNTHESIS OF TRISUBSTITUTED PYRAZOLES WITH POSSIBLE ANTIMICROBIAL ACTIVITY

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Reaction of ketone of [5] with acylhydrazined afforded the hydrazones [6], whereas with arylhydrazines it gave the hydrazones [7], which on boiling with ethanolic HCl produced the pyrazolines [8]. Oxidation of [8] with bromine water furnished the brominated pyrazoles [9]. The reaction [5] with ethyl oxalate gave the ethyl hexenoate [10] which with hydroxylamine afforded the isoxazole ester [11], whereas, with *o*-phenylenediamine gave the oxyquinoxaline [12]. Ester [10], with acylhydrazines afforded the hydrazones [13] which were converted to the *N*-acylpyrazoles [14]. With hydrazines, compound [10] produced the pyrazole-3-esters [15] which were hydrolysed to the acids [16].

Key words: Synthesis, Trisubstituted pyrazoles, Antimicrobial activitiy.

INTRODUCTION

It has been reported that many 3,5-disubstituted-pyrazoles possessed potent hypoglycemic activities [1-10]. The present study which is a continuation of the previous work [11-17], describes the preparation of a number of trisubstituted pyrazoles in the expectation they might possess useful hypoglycemic and/or antimicrobial activity.

Condensation of 2-*p*-bromophenyl-4-formyltriazole [18] (4) with 2-propanone afforded the ketone [5] namely; 4-(2′-*p*-bromophenyltriazol-4′-yl) but-3-en-2-one. Its I.R. spectra showed carbonyl absorption band at 1690 cm^{-1}, whereas, its p.m.r. ($CDCl_3$) spectra displayed the methyl protons as singlet at δ 2.31, (CH=CH) group protons as doublet, doublet at δ 5.25, 5.35 and multiplet signals at δ 7.10-7.85 ppm due to aromatic rings protons. The reaction of [5] with acylhydrazines produced the hydrazones [6]. Their i.r. spectra revealed the carbonyl group absorption of the hydrazone part at 1665-1635 cm^{-1}, bands at 3400-3250 cm^{-1} characteristic for (NH) group, at 1595-1485 cm^{-1} indicative of (C=C, aromatic) and at 1605-1580 cm^{-1} due to (C=N) group. Furthermore, their p.m.r. ($CDCl_3$) spectra displayed the (CH_3) protons as singlet at δ 2.13-2.33, multiplet signals at 6.91-8.31 due to conjugated and aromatic rings protons, and the (NH) proton as singlet at δ 8.51-8.85 ppm. The structure of [6] was further confirmed by measuring the mass spectra of compound (6, R = p-$CH_3OC_6H_4$–) (Table 1).

With arylhydrazines, ketone [5] produced the hydrazones [7]. Their i.r. spectra exhibited bands at 3240-3140 cm^{-1} characteristic for (NH) group and at 1605-1580 cm^{-1} for (C=N) group. Their p.m.r. ($CDCl_3$) spectra gave the (CH_3) protons as singlet at δ 2.0-2.18, multiplet signals at 6.80-8.22 due to conjugated and aromatic rings protons and the (NH) proton as singlet at δ 8.15 ppm. Hydrazones

Table 1. Mass spectral data for compounds (6,R=p-CH_3-OC_6H_4) and (8, R=2, 4$(NO_2)_2C_6H_3$).

Compound	Values of principle m/z fragments relative intensity, (%)
4-(2-*p*-Bromophenyltriazole-4′-yl] but-3-en-2-one-2-*p*-methoxybenzoylhydrazone (6, R - *p*-$CH_3OC_6H_4$–)	439(M, 2), 304($C_{12}H_{11}N_5Br$, 1), 289($C_{12}H_{10}N_4Br$, 1), 171(C_6H_4NBr, 2), 169(C_6H_4NBr, 1) 155(C_6H_4Br, 1), 136(C_8H_8O, 9), 135(C_8H_7O, 100), 107(C_7H_7O, 6), 92(C_6H_4O, 5), 90(C_6N_4N, 4), 77(C_6H_5, 9), 76(C_6H_4, 2) 63(CH_4+HNO_2, 3), 51(C_4H_3, 1), 39(C_3H_3, 2), 28 (CO, 11).
3-Methyl-1-1-(2,4-dinitrophenyl)-5-[2′-*p*-bromophenyltriazol-4′-yl]-2-pyrazoline (8, R=2, 4$(NO_2)_2C_6H_3$–)	471(M, 47), 469(M-2H, 30), 454 ($C_{17}H_9N_7O_4Br$, 13), 439($C_{16}H_6N_7O_4Br$, 16)' 423($C_{18}H_{12}N_6O_2$ Br, 75), 409 ($C_{17}H_{10}N_6O_2Br$, 7), 377($C_{18}H_{12}N_5Br$, 19)' 316 ($C_{12}H_{10}N_7O_4$, 13), 289 ($C_{12}H_{10}$ N_4Br, 11), 276($C_{12}H_{11}N_3Br$, 13)270($C_{12}H_{10}N_6O_2$, 33), 250 ($C_{10}H_9N_3Br$,18), 241($C_{12}H_9N_4O_2$, 16), 228 ($C_8H_{11}N_3Br$, 6), 195($C_6H_3N_4O_4$, 16), 155(C_6H_4-Br, 47), 140($C_9H_4N_2$, 8), 114 (C_8H_4N, 15), 90(C_6H_4N, 100), 80 ($C_4H_4N_2$, 22), 76(C_6H_4, 29), 75(C_6H_3, 32), 63(CH_4+ HNO_2, 64), 52(C_4H_4, 18), 51, (C_4H_3, 15), 39(C_3H_3, 26), 27(HCN, 32).

[7] on refluxing with ethanol containing few drops HCl produced the pyrazolines [8]. Their p.m.r. ($CDCl_3$) spectra displayed the (CH_3) protons as singlet at δ 2.18-2.35, multiplet signals at δ 3.2, due to two protons of H-4-pyrazoline, at 5.4 for one proton of H-5-pyrazoline and at 6.99-8.18 ppm due to aromatic rings protons. The structure of pyrazolines [8] was further confirmed from the mass spectra of compound (8, R = 2,4$(NO_2)_2C_6H_3$–) (Table 1). Oxidation of [8] with an excess of bromine water led to the formation of the brominated pyrazoles [9]. Their p.m.r. ($CDCl_3$) spectra exhibited the (CH_3) protons as singlet at δ 2.31 and the aromatic rings protons as multiplet at 7.12-8.12 ppm, whereas, their uv spectra showed two maxima stretching up to 207 and 289 and one minima up to 239 nm.

Ketone [5] on condensation with ethyl oxalate produced ethyl 2,4-dioxo-6-(2′-*p*-bromophenyltriazol-4′-yl) hex-5-enoate [10]. Its i.r. spectra revealed bands at 1735 cm^{-1} due to the carbonyl ester group, at 1750 cm^{-1} due to α-keto-ester group, at 1650-1500 cm^{-1} indicative of (C=C, aromatic), at 1260-1010 cm^{-1} for (-C-O-C-) of ester group, at 970, 1355, 1370 cm^{-1} for (C-H, aromatic) and the (OH) group band appeared at 3490 cm^{-1}. Whereas, its uv spectra gave two maxima at 210 and 282 and one minima at 242 nm. Its p.m.r. ($CDCl_3$) spectra displayed signals at δ 1.33 (triplet, 3H, $-CH_2CH_3$); 4.28 (quartet, 2H, $-CH_2-CH_3$); 6.22, 6.76 (doublet, doublet, 1H, 1H, -CH=CH-); 6.52 (singlet, 1H, =CH-) and at 7.20-8.22 (multiplet, 6H, OH and aromatic rings protons) ppm. The signal at δ 6.52 ppm proves the enolic form of ester [10] and this explains its reaction with hydrazines to give the pyrazole-3-esters [15] and not the 5-esters.

Ester [10] reacted readily with hydroxylamine to give ethyl 5-[B-(2′-*p*-bromophenyltriazol-4′-yl) vinyl]-isoxazole-3-carboxylate [11], whereas with *o*-phenylenediamine it furnished the oxyquinoxaline [12]. However, on reaction with acylhydrazines, ester [10] furnished the hydrazones [13] which on boiling with ethanol containing few drops of HCl produced the *N*-acylpyrazole esters [14]. The i.r. spectra of [13] showed bands at 1660-1635 cm^{-1} due to carbonyl group of hydrazone part, at 3320-3160 cm^{-1} for (NH) group, at 1725 cm^{-1} for carbonyl ester group, at 1630-1580 indicative of (C=N) group and at 3500 cm^{-1} due to (OH) group. Whereas, the i.r. spectra of [14] revealed carbonyl band of ester group at 1725 and carbonyl group of *N*-acyl part at 1680-1630 cm^{-1}. Furthermore, the reaction of [10] with hydrazines afforded the trisubstituted pyrazole-esters [15]. Formulation of the reaction products as [15] was based on the comparative reactivity of the two carbonyl groups in [10]. The C-2 carbonyl group, being more reactive than the C-4 carbonyl, gets preferably attacked by the nucleophilic reagent such as hydrazine to give the corresponding monohydrazone intermediate which simultaneously undergoes ring closure with the elimination of a water molecule from the imino-proton of hydrazone residue and the hydroxyl group of enolized C-4 carbonyl forming ester [15]. Hydrolysis of the foregoing esters [15] with ethanolic 2N KOH yielded the acids [16]. Their i.r. spectra displayed carbonyl group band at 1720 cm^{-1} and (OH) group absorption at 3500-3400 cm^{-1}

EXPERIMENTAL

Procedure. Central-melting points were determined in open glass capillaries and are uncorrected. IR absorption spectra were recorded with a Unicam SP 1025 recording spectrophotometer using potassium bromide pellets (ν_{max} in cm^{-1}), uv spectra were measured with a Unicam SP 1750 instrument (λ_{max} in nm) in ethanol, and p.m.r. spectra in $CDCl_3$ were taken with a Varian HA 100 instrument. Microanalyses were performed in the Faculty of Science, Cairo University and the mass spectra were measured on a Varian M 66 spectrophotometer.

4-(2′-p-Bromophenyltriazol-4′-yl)but-3-2-one [5]. To a well stirred solution of 2-(*p*-bromophenyl)-4-formyltriazole (4; 1 mmol) [18] in 2-propanone (40 ml) was added drop by drop with a 10 % sodium hydroxide solution (2 ml) for 20 min., and stirring was continued for another 2 hr. The mixture was then acidified with dilute hydrochloric acid, benzene extracted and the benzene layer washed with water then dried. After distillation of the benzene, the ketone [5] was produced as yellowish-brown solid, recrystallized from benzene-methanol mixture, m.p. 90° (yield 75 %). (Anal. Calc. for $C_{12}H_{10}N_3OBr$: C, 49.5; H, 3.4; N, 14.4; Br, 27.2. Found: C, 49.6; H, 3.4; N, 14.3; Br, 27.1). It formed an oxime which crystallized from dilute methanol in pale yellow needles; m.p. 80°. (Anal. Calc. for $C_{12}H_{11}N_4$ OBr: C, 47.1; H, 3.6; N, 18.3; Br, 25.8. Found: C, 47.0; H, 3.9; N, 18.1; Br, 25.8).

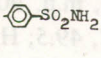
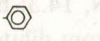
4-(2′-p-Bromophenyltriazol-4′-yl)but-3-en-2-one-2-acyl-[6] or 2-arylhydrazones [7]. A solution of ketone (5; 1 mmol) in ethanol (50 ml) was heated with the desired acyl- or arylhydrazine (1 mmol) for 1 hr, on a boiling water bath. The hydrazones, were recrystallized from methanol or dilute ethanol in needles; yield 25-40 % (Table 2 and 3).

1-Aryl-3,5-disubstituted-2-pyrazolines [8]. These were obtained by refluxing the appropriate arylhydrazones (7; 1 mmol) in ethanol (25 ml) with HCl (1 ml) for 1 hr. They were recrystallized from ethanol in needles, yield 28-35 % (Table 4).

Table 2. Microanalytical data for 4-(2'-*p*-bromophenyltriazol-4'-yl)but-3-en-2-one-2- acylhydrazones [6].

R	Yield %	M.p. °C	Molecular formula	Calculated (%) C	H	N	Br	Found (%) C	H	N	Br
$-CH_2CN$	25	208	$C_{15}H_{13}N_6OBr$	48.4	3.5	22.6	21.2	48.4	3.6	22.7	21.1
	35	232	$C_{19}H_{17}N_6OBr$	53.8	4.0	19.8	18.6	53.7	4.0	19.9	18.5
	30	212	$C_{20}H_{18}N_5OBr$	56.7	4.3	16.6	18.7	56.6	4.4	16.7	18.7
	35	230	$C_{19}H_{15}N_6O_3Br$	50.2	3.3	18.5	17.4	50.0	3.4	18.4	17.6
	33	222	$C_{19}H_{15}N_5OBr_2$	46.8	3.1	14.4	32.4	46.8	3.3	14.5	32.4
	30	180	$C_{20}H_{18}N_5OBr$	56.7	4.3	16.6	18.7	56.7	4.2	16.5	18.8
	30	197	$C_{19}H_{16}N_5OBr$	55.8	3.9	17.1	19.3	55.9	3.9	17.0	91.1
	32	225	$C_{19}H_{15}N_5OBrCl$	51.4	3.4	15.8	17.8	51.3	3.5	16.0	17.7
	30	239	$C_{20}H_{18}N_5O_2Br$	54.7	4.1	16.0	18.0	54.5	4.2	15.9	18.1
	32	131	$C_{19}H_{15}N_5OBrCl$	51.4	3.4	15.8	17.8	51.3	3.5	15.7	17.7
	35	148	$C_{19}H_{14}N_7O_5Br$	45.7	2.8	19.6	15.8	45.5	3.0	19.6	15.9

Table 3. Micronalytical data for 4-(2'-*p*-bromophenyltriazol-4'-yl)but-3-en-2-one-2-arylhydrazones [7].

R	Yield %	M.p. °C	Molecular formula	Calculated (%) C	H	N	Br	Found (%) C	H	N	Br
	35	160	$C_{18}H_{17}N_6O_2SBr$	47.0	3.7	18.3	17.2	47.1	3.8	18.1	17.1
	35	87	$C_{18}H_{16}N_5Br$	56.7	4.2	18.4	20.7	56.7	4.3	18.5	20.6
	40	178	$C_{18}H_{15}N_6O_2Br$	50.7	3.5	19.7	18.6	50.6	3.6	19.5	18.7
	40	170	$C_{18}H_{14}N_7O_4Br$	45.9	3.0	20.8	16.8	46.0	3.1	20.6	16.9

1-Aryl-4-bromo-3,5-disubstituted pyrazoles [9]. A suspension of (8; 3 mmol) in water (30 ml) were treated gradually with continuous stirring with 5 % bromine water (30 ml) for 8 hr. They were recrystallized from dilute methanol in needles; yield 25–30 % (Table 5).

Ethyl 2,4-dioxo-6-(2'-p-bromophenyltriazol-4'-yl)hex-5-enoate [10]. It was prepared by condensation of ketone (5, 0.1 mol) and ethyl oxalate (0.1 mol) in dry ether (250 ml) in the presence of sodium ethoxide (0.1 mol). After keeping the reaction mixture at room temperature for 24 hr, the separated yellow sodium salt was filtered off, washed with ether, dried and then acidified with cooled dilute sulphuric acid. It was purified by recrystallization from benzene-methanol mixture in yellowish-brown needles, m.p. 106°; yield 45 %. (Anal. Calc. for $C_{16}H_{14}N_3O_4Br$: C, 49.1; H, 3.6; N, 10.7, Br, 20.2. Found: C, 49.0; H, 3.8; N, 10.5, Br, 20.3).

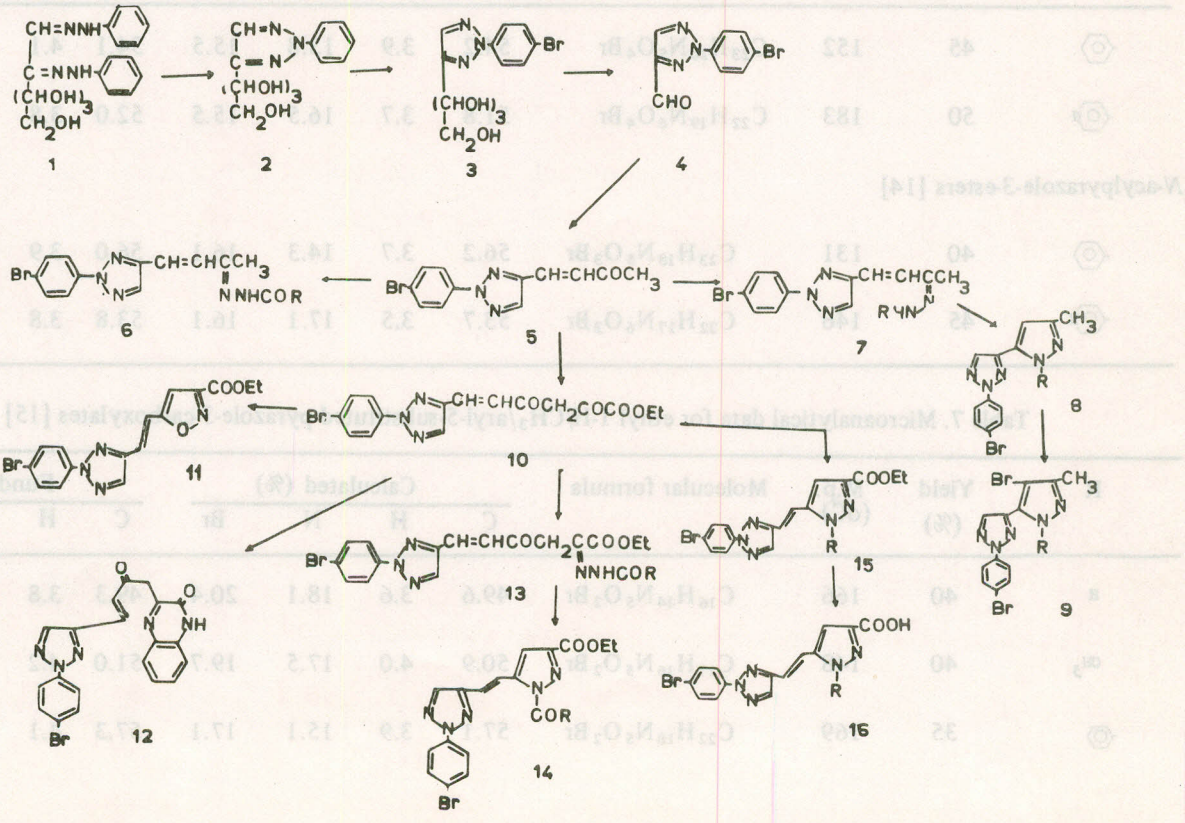
Table 4. Microanalytical data for 1-aryl-3-methyl-5-(2′-*p*-bromophenyltriazol-4′-yl)-2-pyrazolines [8].

R	Yield %	M.p. °C	Molecular formula	Calcualted(%) C	R	N	Br	Found (%) C	H	N	Br
	30	185	$C_{18}H_{17}N_6O_2SBr$	47.0	3.7	18.3	17.2	47.0	3.8	18.5	17.2
	28	120	$C_{18}H_{16}N_5Br$	56.7	4.2	18.4	20.7	56.7	4.3	18.5	20.8
	30	148	$C_{18}H_{16}N_5O_2Br$	52.3	3.9	17.0	19.1	52.1	3.9	17.1	19.0
	35	208	$C_{18}H_{15}N_6O_2Br$	50.7	3.5	19.7	18.6	50.5	3.8	19.7	18.3
	35	245	$C_{18}H_{14}N_7O_4Br$	45.9	3.0	20.8	16.8	45.8	3.2	20.8	16.7

Table 5. Microanalytical data for 1-aryl-4-bromo-3,5-disubstituted pyrazoles [9].

R	Yield %	M.p. °C	Molecular formula	Calculated (%) C	H	N	Br	Found (%) C	H	N	Br
	25	183*	$C_{18}H_{12}N_5Br_3$	40.2	2.2	13.0	44.6	40.0	2.3	13.1	44.5
	30	210**	$C_{18}H_{12}N_6O_2Br_2$	42.9	2.4	16.7	31.8	42.7	2.5	16.6	31.8

* lit. M.p. 183°; ** lit. M.p. 210°.



Ethyl 5-substituted-isoxazole-3-carboxylate [11]. This compound was prepared by boiling hexenoate (10; 1 g) in ethanol (25 ml) with hydroxylamine hydrochloride (0.4 g) and sodium acetate (0.5 g) in water (3 ml) for 2 hr. It was recrystallized form dilute ethanol in brown needles, m.p. 130°, yield 40 %. IR: 1720 cm^{-1} (C=O). (Anal. Calc. for $C_{16}H_{13}N_4O_3Br$: C, 49.5; H, 3.4; N, 14.4; Br, 20.4. Found: C, 49.3; H, 3.5; N, 14.4; Br, 20.3).

Oxyquinoxaline derivative [12]. A mixture of ester (10; 1 mmol) and *o*-phenylenediamine (1 mmol) in ethanol (50 ml) was heated under reflux for 2 hr. It was recrystallized from ethanol in brown needles, m.p. 194°, yield 70 %. (Anal. Calc. for $C_{20}H_{14}N_5O_2Br$: C, 55.2; H, 3.2; N, 16.1; Br, 18.2. Found: C, 55.2; H, 3.3; N, 16.3; Br, 18.0).

Ethyl 2,4-dioxo-6-(2'-p-bromophenyltriazol-4'-yl) hexenoate 2-acylhydrazones [13]. An ethanolic solution (50 ml) of the appropriate acylhydrazine (1 mmol) was added to a cold solution of the ethyl hexenoate (10; 1 mmol) in ethanol (75 ml) containing two drops of glacial acetic acid and the reaction mixture left at room temperature for 24 hr. They were recrystallized from chloroform-light petroleum (b.p. 40-60°) in needles, yield 45-50 % (Table 6).

1-Acyl-3-carbethoxy-5-B-(2'-p-bromophenyltriazol-4'-yl)-vinyl) pyrazoles [14]. Hydrazones (13; 0.5 g) were boiled with ethanol 100 ml) containing two drops of HCl for 1 hr. The acylpyrazole esters were recrystallized from dilute methanol in needles, yield 40-45 % (Table 6).

Ethyl 1-H/CH_3/aryl-5-substituted-pyrazoles-3-carboxylates [15]. These pyrazole esters were obtained by refluxing ester (10; 1 mmol) with the appropriate hydrazine, methyl or arylhydrazines (1 mmol) in ethanol (50 ml) for 3 hr. They were recrystallized from ethanol in needles; yield 45-55 % (Table 7).

1-H/CH_3/Aryl-5-substituted pyrazole-3-carboxylic acids (16). The foregoing pyrazole esters (15; 0.5 g) was refluxed with ethanolic 2N KOH solution (25 ml) on a steam bath for 3 hr. They were recrystallized from dilute ethanol in needles, yield 50-60 % (Table 8).

Table 6. Microanalytical data for ethyl 2,4-dioxo-6-substituted hex-5-enoate-2-acylhydrazones [13], and ethyl 1-acyl-5-substituted-pyrazole-3-carboxylates [14].

R	Yield (%)	M.p. (°C)	Molecular formula	Calcualted (%)				Found (%)			
				C	H	N	Br	C	H	N	Br
	45	152	$C_{23}H_{20}N_5O_4Br$	54.2	3.9	13.8	15.5	54.1	4.1	13.6	15.6
	50	183	$C_{22}H_{19}N_6O_4Br$	51.8	3.7	16.5	15.5	52.0	3.8	16.5	15.3
N-acylpyrazole-3-esters [14]											
	40	131	$C_{23}H_{18}N_5O_3Br$	56.2	3.7	14.3	16.1	56.0	3.9	14.1	16.0
	45	146	$C_{22}H_{17}N_6O_3Br$	53.7	3.5	17.1	16.1	53.8	3.8	17.3	16.0

Table 7. Microanalytical data for ethyl 1-H/CH_3/aryl-5-substituted pyrazole-3-carboxylates [15].

R	Yield (%)	M.p. (oC)	Molecular formula	Calculated (%)				Fund (%)			
				C	H	N	Br	C	H	N	Br
H	40	166	$C_{16}H_{14}N_5O_2Br$	49.6	3.6	18.1	20.4	49.3	3.8	18.0	20.5
CH_3	40	148	$C_{17}H_{16}N_5O_2Br$	50.9	4.0	17.5	19.7	51.0	4.2	17.3	19.8
	35	169	$C_{22}H_{18}N_5O_2Br$	57.1	3.9	15.1	17.1	57.3	4.1	14.9	17.0

(Continued.....)

(Table7 continued)

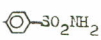
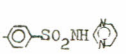
	35	170	$C_{23}H_{20}N_5O_2Br$	57.9	4.2	14.7	16.6	58.0	4.3	15.0	16.4
	40	196	$C_{22}H_{19}N_6O_4SBr$	48.7	3.5	15.5	14.6	48.5	3.7	15.4	14.8
	30	169	$C_{21}H_{17}N_6O_2Br$	54.3	3.7	18.1	17.0	54.3	3.9	18.0	17.3
	40	171	$C_{26}H_{21}N_8O_4SBr$	50.3	3.4	18.1	12.7	50.0	3.6	18.3	12.4
	40	144	$C_{24}H_{18}N_7O_2Br$	55.9	3.5	19.0	15.3	55.8	3.8	19.2	15.0

Table 8. Microanalytical data for 1-H/CH_3/aryl-5-substituted-pyrazole-3-carboxylic acids [16].

R	Yield (%)	M.p. (^oC)	Molecular formula	Calculated (%)				Fund (%)			
				C	H	N	Br	C	H	N	Br
H	50	98	$C_{14}H_{10}N_5O_2Br$	46.8	2.8	19.5	22.0	46.5	3.0	19.6	22.1
CH_3	50	92	$C_{15}H_{12}N_5O_2Br$	48.3	3.2	18.8	21.2	48.2	3.5	19.0	21.0
	55	116	$C_{20}H_{14}N_5O_2Br$	55.2	3.2	16.1	18.2	55.0	3.5	16.3	18.0
	60	190	$C_{20}H_{15}N_6O_4SBr$	46.7	2.9	16.3	15.4	46.4	3.0	16.0	15.5
	60	188	$C_{24}H_{17}N_8O_4SBr$	48.7	2.9	18.9	13.4	48.5	3.1	19.0	13.3
	56	166	$C_{19}H_{13}N_6O_2Br$	52.3	3.0	19.3	18.1	52.1	3.3	19.3	18.1
	55	164	$C_{22}H_{14}N_7O_2Br$	54.2	2.9	20.1	16.2	54.0	3.1	20.2	16.1

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