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Synthesis, Antiinflammatory, Antioxidant and Antibacterial Activities of 7-Methoxy Benzofuran Pyrazoline Derivatives

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Chalcones were prepared from 2-acetyl-7-methoxy benzofuran and condensed with different aromatic acid hydrazides to get corresponding pyrazolines. The structures of all these compounds have been established on the basis of analytical and spectral data. Compounds have been screened for antiinflammatory, antioxidant and antibacterial activities. Among seven compounds that were screened for antiinflammatory activity, compounds **4g** and **5m** showed 83.89 and 80.49 % inhibition, respectively of oedema volume, while the standard drug (ibuprofen) showed inhibition of 91.93 %. Compounds **4k** and **5h** showed moderate activity 72.79 and 59.57 %. The values are statistically significant against the control at $p < 0.05$. All the 30 compounds were screened for antioxidant activity at 250, 100 50, 25 and 10 µg concentration against standard drug ascorbic acid. Compounds **4g, 4h, 4k, 4m, 5g, 5h, 5k** and **5m** showed excellent antioxidant activity as compared with ascorbic acid. Among 30 compounds that were screened against two gram +ve (*S. aureus* and *B. subtilis*) and two gram -ve (*E. coli* and *P. aeruginosa*) organisms, compounds possessing *p*-chloro, *p*-fluoro,2-amino-5-bromo,2-hydroxy-5-nitro and 3,5-dichloro on phenyl ring showed good activity against *E. coli* and *B. subtilis* and the activity is comparable with that of standard drug ciprofloxacin.

Key Words: 2-Acetyl-7-methoxy benzofuran, Pyrazolines, Acid hydrazides, Chalcones, Antiinflammatory, Antioxidant, Antimicrobial activities.

INTRODUCTION

Benzofuran[1,2] derivatives have been reported for sedative and hypnotic, anticonvulsant, CNS stimulant, antibacterial, antifungal and antiinflammatory[3] activities, *etc*. On the basis of the biological activity exhibited by such natural products, numerous synthetic analogues were prepared to improve their biological activities. It has been established in some cases

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such as morphine, furocoumarins (psoralin and angelicin), furochromones (Khellin and visnagin) and coumestrol that furan ring is an essential part for biological activity[4].

Pyrazoles, pyrazolines[5] and pyrazolidines form the interesting class of compounds. Drugs having pyrazole and pyrazoline ring systems are well known for their antimicrobial, CNS depresent, anticonvulsant, antiinflammatory, antioxidant, hypoglycemic, hypotensive, anti-carcinogenic activities etc. In view of the above facts, in present study, the synthesis of 7-methoxy benzofuran pyrazolines is proposed by condensing different benzofuran chalcones with different acid hydrazides. All the synthesized compounds were screened for antiinflammatory, antioxidant and antibacterial activities.

EXPERIMENTAL

The UV spectra of the compounds were recorded on double beam Shimadzu 160-Graphicord spectrometer, IR spectra were recorded on Shimadzu-FTIR 8300 by KBr disc method. ^{1}H NMR were recorded on AMX-400 liquid state spectrometer at 440 MHz in $CDCl_3$ using TMS as internal standard. Mass spectra were measured on FAB mass spectrometer. Melting points were recorded in open capillary tubes in Toshniwal melting point apparatus and were uncorrected. TLC was performed on micro TLC plate, supplied by E. Merck and detection was done with iodine.

Preparation of 2-[(4´-oxyacetic acid)-phenyl propeneone)]-7-methoxy benzofuran (IIp, IIm) (Chalcone): The mixture of 2-acetyl-7-methoxy benzofuran (0.01 M) were added drop wise to a solution of sodium hydroxide/potassium hydroxide (8 mL, 10 % NaOH in water), well-stirred and p/m formyl phenoxy acetic acid (0.01 M) in ethanol (20 mL) at room temperature, method of aldol condensation reaction was followed. The solution was stirred at room temperature for 24 h by using magnetic stirrer. The reaction mixture was diluted with ice-cold water and then acidified with HCl. The obtained product was filtered and washed with ice-cold water and double recrystallized from aqueous ethanol. The purity of the compound was checked by TLC and melting point. IR (KBr, cm^{-1}, ν_{max}): 2923 (C-H, str.), 1735 (C=O, str., COOH), 1660 (C=O, str), 1548 (C=C, str.), 1139 (C-O-C, str.), 750 (C-H, Out of plane bending), 1014 (C-H, in plane bending). ^{1}H NMR, $CDCl_3$, δ: 3.85 (s, 3H, $-OCH_3$), 4.5-5.5 (t, 1H, N-CH-Ar); 4.6-4.9 (2s, 2H of OCH_2COOH); 5.98 (d, 1H, -CO-CH), 6-9 (m, 14H, Ar-H), 8.40 (d, 1H, =CH-Ar) 10.5 (s, 1H of COOH). Mass, m/z: 352, 277, 201, 147, 105, 90, 78, 63.

Preparation of 2-[5′-phenyl(4″-oxyacetic acid)-1-aryl ketano pyrazoline)]-7-methoxy benzofuran[6-8] (IIIp, IIIm): Chalcone (**IIp, IIm**) (0.01 M) and aromatic acid hydrazide (0.02 M) were taken in 20 mL of

glacial acetic acid and refluxed above 130ºC for a period of 10 h. The reaction mixture was concentrated and poured into 300 mL of ice-cold water and recrystallized from aqueous ethanol. The purity of the compound was checked by TLC and melting point. IR (KBr, cm^{-1}, ν_{max}): 1735 (C=O, str., COOH), 1662 (N-C=O, str.), 1608 (C=N, str.), 1548 (C=C, str.), 1139 (C-O-C, str.), 713, 750 (out of plane bending). ^1H NMR, $CDCl_3$, δ: 3.1-3.5 (d, 2H, CH_2 of pyrazoline), 3.85 (s, 3H, $-OCH_3$), 4.5-5.5 (t, 1H, N-CH-Ar); 10.5 (s, 1H of COOH), 6-9 (m, 14H, Ar-H), 4.9-4.9 (2s, 2H of OCH_2COOH). Mass, m/z: 470, 366, 292, 278, 239, 216, 188, 174, 148, 105, 90, 78, 63. Physical data are shown in Table-1.

Antiinflammatory activity

Carrageenan induced rat hind paw oedema method[9,10]:

Male albino rats weighing between 100-200 g, individually housed, provided with adequate food and water. They are divided into various groups. These animals were used for antiinflammatory studies. Six pyrazoline derivatives were screened for antiinflammatory activity. The toxicity studies were performed and found, no visible toxic symptoms were observed for the first 2 h and no death was reported after 24 h. Among various doses, 2000 mg/kg body weight was observed as safe dose, the 1/10th of 2000 mg/kg body weight *i.e.*, 200 mg/kg body weight was fixed as the dose of acute antiinflammatory screening[11-14].

The method of Winter *et al.*[15] was used with slight modification. The apparatus used for measurement of rat paw volume was that of Butle *et al.* modified by Sharma *et al*.[16] The animals were divided into 8 groups of 6 animals each. 1 group served as a standard (ibuprofen) and another group served as control (1 % CMC) and rest of the groups were used for the test drugs. Food was withdrawn overnight with adequate water before the experiment. The drugs were given orally. After 1 h, a sub plantar injection of 0.05 mL of 1 % carrageenan was administered. The volume of the injected paw was measured with a plethysmograph immediately. The paw volume was again measured after 3 h. The average paw volume in a group of drug treated rats were compared with that of a group with vehicle (control group) and the percentage inhibition of oedema was calculated the forumula.

$$\% \text{ inhibition} = (1 - Vt/Vc) \times 100,$$

where, Vt = mean volume of the test drug, Vc = mean volume of the control. The results are shown in Table-2.

Antioxidant activity[17,18]

All drugs have been diluted in 95 % ethanol to get 250, 100, 50, 25, 10 μg/mL concentrations. DPPH solution (2 μ mol) has been prepared by 95% ethanol. Then 0.5 mL of drug solution and 0.5 mL of DPPH solution (freshly prepared) were added. 0.5 mL of DPPH solution and 0.5 mL of

TABLE-1
PHYSICAL DATA OF 7-METHOXY BENZOFURAN
PYRAZOLINE DERIVATIVES

Compd.	Ar	m.f.	m.p. (ºC)	λ_{max}	Yield (%)	R_f value
PY-1A	Phenyl	$C_{27}H_{22}N_2O_6$	96-98	297	62	0.60
PY-2A	4-Hydroxy phenyl	$C_{27}H_{22}N_2O_7$	85-90	307	45	0.90
PY-3A	4-Chloro phenyl	$C_{27}H_{21}N_2O_6Cl$	80-85	299	75	0.66
PY-4A	2-Chloro phenyl	$C_{27}H_{21}N_2O_6Cl$	106-108	297	78	0.70
PY-5A	4-Nitro phenyl	$C_{27}H_{21}N_3O_8$	95-97	306	63	0.82
PY-6A	2-Nitro phenyl	$C_{27}H_{21}N_3O_8$	93-96	308	32	0.88
PY-7A	4-Fluoro phenyl	$C_{27}H_{21}N_2O_6F$	89-93	308	57	0.87
PY-8A	*o*-Tolyl	$C_{28}H_{24}N_2O_6$	120-122	308	67	0.80
PY-9A	2-Hydroxy phenyl	$C_{27}H_{22}N_2O_7$	80-83	296	68	0.89
PY-10A	4-Amino phenyl	$C_{27}H_{23}N_3O_6$	120-122	295	54	0.83
PY-11A	Isonicotinyl	$C_{27}H_{22}N_3O_6$	98-102	307	58	0.78
PY-12A	4-Methoxy phenyl	$C_{28}H_{23}N_2O_7$	89-92	307	72	0.85
PY-13A	2-Amino-5-bromo phenyl	$C_{27}H_{22}N_3O_6Br$	116-120	308	76	0.90
PY-14A	2-Hydroxy-5-nitro phenyl	$C_{27}H_{21}N_3O_9$	123-125	309	66	0.89
PY-15A	3,5-Dichloro phenyl	$C_{27}H_{20}N_2O_6Cl_2$	100-112	315	62	0.75
PY-1B	Phenyl	$C_{27}H_{22}N_2O_6$	100-103	306	60	0.62
PY-2B	4-Hydroxy phenyl	$C_{27}H_{22}N_2O_7$	90-93	293	42	0.89
PY-3B	4-Chloro phenyl	$C_{27}H_{21}N_2O_6Cl$	91-93	299	73	0.65
PY-4B	2-Chloro phenyl	$C_{27}H_{21}N_2O_6Cl$	100-105	308	73	0.70
PY-5B	4-Nitro phenyl	$C_{27}H_{21}N_3O_8$	90-94	307	35	0.82
PY-6B	2-Nitro phenyl	$C_{27}H_{21}N_3O_8$	89-91	307	52	0.87
PY-7B	4-Fluoro phenyl	$C_{27}H_{21}N_2O_6F$	115-120	307	67	0.86
PY-8B	*o*-Tolyl phenyl	$C_{28}H_{24}N_2O_6$	118-120	308	68	0.80
PY-9B	2-Hydroxy phenyl	$C_{27}H_{22}N_2O_7$	89-90	306	69	0.82
PY-10B	4-Amino phenyl	$C_{27}H_{23}N_3O_6$	116-118	309	72	0.83
PY-11B	Isonicotinyl	$C_{27}H_{22}N_3O_6$	113-115	309	70	0.78
PY-12B	4-Methoxy phenyl	$C_{28}H_{23}N_2O_7$	96-99	307	32	0.85
PY-13B	2-Amino-5-bromo phenyl	$C_{27}H_{22}N_3O_6Br$	112-116	307	35	0.90
PY-14B	2-Hydroxy-5-nitro phenyl	$C_{27}H_{21}N_3O_9$	120-122	308	64	0.89
PY-15B	3,5-Dichloro phenyl	$C_{27}H_{20}N_2O_6Cl_2$	113-116	306	60	0.74

ethanol were used as control. Reaction mixture was allowed for 20 min. UV absorbance was measured at 517 nm. The percentage of scavenging has been calculated by the equation given below. Ascorbic acid was used as standard drug. The results are shown in Table-3.

Antibacterial studies[19-21]

Cup-plate method[22-25]

The drug (**IIp, IIm**) were dissolved in DMF to produce 10 and 25 µg/mL concentrations. Both the concentrations were used in the antibacterial assay. Ciprofloxacin was used as the reference standard at 10 µg/mL

TABLE-2
ANTIINFLAMMATORY STUDIES

Drug code	Dosage (mg/kg)	Mean oedema volume ± S.E. (0-3 h)	Reduction in oedema volume (%)
Control		0.42 ± 0.192	
Ibuprofen	200	0.0416 ± 0.017	91.13
PY-2B	200	0.27 ± 0.17[a]	40.39
PY-3A	200	0.26 ± 0.19[a]	32.89
PY-5A	200	0.28 ± 0.171[a]	40.14
PY-7A	200	0.75 ± 0.03[a]	83.89
PY-8B	200	0.12 ± 0.049[a]	72.79
PY-11A	200	0.19 ± 0.077[a]	59.57
PY-13B	200	0.09 ± 0.037[a]	80.49

One-way Anova followed by schiffe's post hoc test.
Allowance value = 0.239, [a] = $p < 0.05$ (Vs) control.
Note: Any two means showing difference of 0.239 are statistically significant.

concentration. The microorganisms used were gram positive *Staphylococcus aureus* and *Bacillus subtilis*, gram negative *Pseudomonas aeruginosa* and *Escherichia coli*.

The sterile nutrient agar medium was melted and inoculated with 16-18 h old broth culture at 1 % level. The inoculation has to be completed under aseptic conditions and when the medium was in molten state. The inoculated medium was transferred to sterile petridishes, evenly distributed and allowed to solidify. Thereafter the cups (8 mm diameter) were made by punching into the agar surface with a sterile cork borer and scopping out the punched part of the agar. In each of these cups, 0.05 mL (50 µg) of the test compound/reference standard was added using a micropipette. The plates were incubated at 37ºC for 16 h and the zone of inhibition was measured. The results are shown in Table-4.

RESULTS AND DISCUSSION

All the synthesized compounds were in conformity with the structures envisaged. The structures are confirmed on the basis of physical and spectral data *viz.*, IR, ^{1}H NMR and Mass spectroscopy. The chalcones (*p*- and *m*-) (**II**) were prepared from 2-acetyl-7-methoxy benzofuran and with *p*-formyl phenoxy acetic acid and *m*-formyl phenoxy acetic acid, respectively in the presence of strong alkali (10 % aqueous NaOH/KOH). The structures of the chalcones were confirmed by TLC, melting point and IR spectral data. Benzofuran pyrazolines(III) (PY-1A to PY-15A) & (PY+1B to PY-15B) were synthesized by cyclic condensation of chalcones with different acid hydazides (AH1-AH15) in presence of glacial acetic acid (**Scheme-I**). The structures of the synthesized compounds were confirmed on the basis of physical data and IR, NMR and Mass spectral data. The spectral data was correlating with the proposed structures.

TABLE-3

ANTIOXIDANT ACTIVITY OF 7-METHOXY BENZOFURAN PYRAZOLINE DERIVATIVES

	Control	10 µg	25 µg	50 µg	100 µg	250 µg
Std. (AS %)	0.100 ± 0.1920	0.06 ± 0.017 (40.00)	0.029 ± 0.037 (71.00)	0.020 ± 0.171 (80.00)	0.018 ± 0.19 (82.00)	0.012 ± 0.03 (88.00)
PY-1A	0.130 ± 0.0920	0.12 ± 0.117 (7.69)	0.11 ± 0.037 (15.38)	0.01 ± 0.071 (23.00)	0.09 ± 0.019 (30.00)	0.088 ± 0.03 (32.00)
PY-13A	0.100 ± 0.0920	0.08 ± 0.117 (20.00)	0.06 ± 0.007 (40.00)	0.030 ± 0.071 (70.00)	0.025 ± 0.19 (75.00)	0.022 ± 0.03 (78.00)
PY-7A	0.101 ± 0.1920	0.06 ± 0.17 (39.62)	0.059 ± 0.037 (50.49)	0.04 ± 0.171 (60.39)	0.03 ± 0.19 (40.59)	0.0162 ± 0.03 (83.96)
PY-2A	0.101 ± 0.1920	0.089 ± 0.017 (11.88)	0.083 ± 0.037 (17.82)	0.069 ± 0.171 (31.68)	0.06 ± 0.19 (40.59)	0.061 ± 0.03 (49.50)
PY-8A	0.110 ± 0.0192	0.093 ± 0.01 (15.45)	0.049 ± 0.027 (60.27)	0.03 ± 0.0171 (72.72)	0.02 ± 0.19 (81.81)	0.0158 ± 0.03 (85.63)
PY-3A	0.101 ± 0.1120	0.075 ± 0.117 (28.21)	0.07 ± 0.02 (30.69)	0.071 ± 0.0171 (30.69)	0.0571 ± 0.029 (43.46)	0.042 ± 0.04 (58.41)
PY-11A	0.100 ± 0.0192	0.08 ± 0.0017 (20.00)	0.061 ± 0.137 (40.00)	0.031 ± 0.0171 (70.00)	0.0171 ± 0.019 (82.82)	0.0176 ± 0.013 (82.36)
PY-5A	0.110 ± 0.1520	0.09 ± 0.02 (18.18)	0.08 ± 0.047 (27.27)	0.06 ± 0.0171 (45.45)	0.052 ± 0.19 (52.27)	0.05 ± 0.022 (54.54)
PY-1B	0.140 ± 0.0190	0.012 ± 0.01 (14.28)	0.102 ± 0.02 (26.42)	0.101 ± 0.0171 (27.85)	0.099 ± 0.19 (29.28)	0.09 ± 0.03 (35.71)
PY-7B	0.101 ± 0.1620	0.08 ± 0.011 (20.79)	0.059 ± 0.02 (41.58)	0.04 ± 0.0171 (60.39)	0.028 ± 0.19 (66.36)	0.017 ± 0.03 (83.16)
PY-2B	0.130 ± 0.1920	0.0142 ± 0.01 (6.15)	0.11 ± 0.026 (15.38)	0.10 ± 0.0171 (23.07)	0.09 ± 0.191 (30.76)	0.088 ± 0.031 (32.30)
PY-8B	0.120 ± 0.0190	0.098 ± 0.01 (19.00)	0.08 ± 0.02 (33.88)	0.075 ± 0.017 (38.01)	0.05 ± 0.19 (58.67)	0.04 ± 0.03 (66.94)
PY-3B	0.110 ± 0.1600	0.09 ± 0.011 (18.18)	0.088 ± 0.027 (20.00)	0.07 ± 0.017 (36.36)	0.05 ± 0.190 (54.54)	0.042 ± 0.06 (16.81)
PY-11B	0.101 ± 0.0192	0.08 ± 0.06 (20.79)	0.059 ± 0.02 (41.58)	0.04 ± 0.017 (36.36)	0.03 ± 0.18 (70.29)	0.02 ± 0.03 (80.19)
PY-5B	0.130 ± 0.1920	0.122 ± 0.01 (6.15)	0.01 ± 0.02 (23.07)	0.09 ± 0.0171 (30.76)	0.088 ± 0.19 (32.30)	0.08 ± 0.03 (38.46)

TABLE-4
ANTIBACTERIAL ACTIVITY OF BENZO FURO PYRAZOLINE DERIVATIVES

Compound code	Amount of drug per cup (µg)	Zone of inhibition (mm)			
		S. aureus	*B. subtilis*	*E. coli*	*P. aeuroginosa*
PY-1A	10	12	-	-	-
	25	14	-	-	-
PY-2A	10	13	-	14	11
	25	14	-	15	12
PY-3A	10	14	16	12	-
	25	15	18	13	-
PY-4A	10	-	-	-	-
	25	-	-	-	-
PY-5A	10	14	14	14	-
	25	15	16	15	-
PY-6A	10	-	-	-	-
	25	-	-	-	-
PY-7A	10	14	16	12	12
	25	15	18	16	13
PY-8A	10	-	-	-	-
	25	-	-	-	-
PY-9A	10	-	-	-	-
	25	-	-	-	-
PY-10A	10	-	-	-	-
	25	-	-	-	-
PY-11A	10	11	10	10	-
	25	12	12	11	-
PY-12A	10	-	-	-	-
	25	-	-	-	-
PY-13A	10	13	15	13	-
	25	14	17	15	-
PY-14A	10	12	16	14	-
	25	13	17	16	-
PY-15A	10	-	14	17	-
	25	-	17	17	-
Standard	10	21	20	20	19
PY-1B	10	10	-	-	-
	25	11	-	-	-
PY-2B	10	12	-	13	10
	25	13	-	14	11
PY-3B	10	12	14	10	-
	25	14	15	12	-
PY-4B	10	-	-	-	-
	25	-	-	-	-
PY-5B	10	14	14	14	-
	25	15	16	15	-

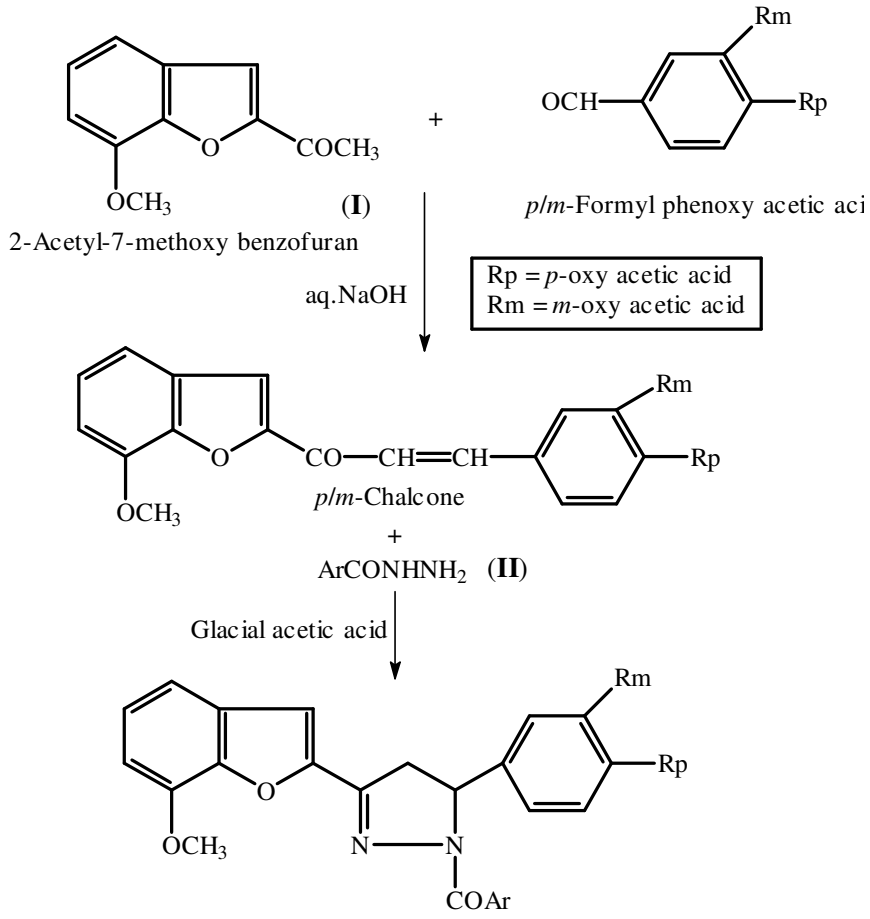
Compound code	Amount of drug per cup (µg)	Zone of inhibition (mm)			
		S. aureus	*B. subtilis*	*E. coli*	*P. aeuroginosa*
PY-6B	10	-	-	-	-
	25	-	-	-	-
PY-7B	10	14	16	12	12
	25	15	18	16	13
PY-8B	10	-	-	-	-
	25	-	-	-	-
PY-9B	10	-	-	-	-
	25	-	-	-	-
PY-10B	10	-	-	-	-
	25	-	-	-	-
PY-11B	10	11	10	10	-
	25	12	12	11	-
PY-12B	10	-	-	-	-
	25	-	-	-	-
PY-13B	10	11	12	14	-
	25	12	13	16	-
PY-14B	10	10	14	13	-
	25	11	16	17	-
PY-15B	10	-	14	13	-
	25	-	16	16	-
Standard	10	21	20	20	19

'-' resistant; standard drug is ciprofloxacin

Among the 30 compounds, 7 compounds were screened for anti-inflammatory activity using Carrageenan induced paw oedema method. While the standard drug (ibuprofen) has shown inhibition of 91.93 %, the compounds PY-7A and PY-13B showed 83.89 and 80.49 % inhibition of oedema, respectively. Compounds PY-8B and PY-11A showed moderate activity (72.79 and 59.57 %). The above compounds were found to be statistically significant against control at $p < 0.05$. The fairly good activity of compound PY-7A and PY-13B might be attributed due to the presence of *p*-fluoro and 2-amino groups.

Out of 30 compounds PY-7A, PY-13A, PY-8A, PY-11A, PY-7B, PY-8B, PY-11B, PY-13B have exhibited good antioxidant activity which is comparable with that of standard drug ascorbic acid. This may be due to 5-bromo groups on the phenyl ring.

All the synthesized compounds were screened against two gram +ve (*Staphylococcus aureus, Bacillus subtilis*) and two gram -ve (*Pseudomonas aeuruginosa, E. coli*) bacteria. The study was carried out by cup-plate method using Muller Hington media. Ciprofloxacin was used as a standard drug at a concentration of 10 µg per cup. All the compounds were used at a concentration of 10 and 25 µg per cup. Compounds PY-1A, PY-2A,



p/m-7-Methoxy benzofuro prrazoline derivatives

(**III**)

(PY1A-PY15A, PY1B-PY15B)

Scheme-I

PY-3A, PY-5A, PY-7A, PY-3B and PY-7B have shown moderate activity against *Staphylococcus aureus* as compared with standard. Compounds PY-3A, PY-5A, PY-7A, PY-13A, PY-14A, PY-15A, PY-5B, PY-7B, PY-13B, PY-14B and PY-15B have shown fairly good activity against *Bacillus subtilis* at a concentration of 25 μg. Only PY-7A and PY-7B shown little activity against *Pseudomonas aeuroginosa*. Among the 30 compounds, PY-2A, PY-5A, PY-7A, PY-13A, PY-14A, PY-15A, PY-2B, PY-5B, PY-7B, PY-13B and PY-15B have shown fairly good activity against *E. coli*. The good activity of the compounds against *B. subtilis* and *E. coli* might attributed to the presence of *p*-chloro, *p*-fluoro, 2-amino-5-bromo, 2,5-dinitro and 2,5-

dichloro substituents on phenyl ring. From this data, it is very vclear that pyrazolines of benzofuran, if suitably substituted might show good activity against *B. subtilis* and *E. coli*.

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