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Synthesis of some new 1,3,5-trisubstituted pyrazoles as antioxidant and antiinflammatory agents

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ABSTRACT

A series of some new 1,3,5-trisubstituted pyrazoles was synthesized by the reaction of α-β dibromochalcones with phenylhydrazine hydrochloride. α-β-Dibromochalcones were prepared by the regioselective bromination of respective chalcones with tetrabutylammonium tribromide. The synthesized trisubstituted pyrazoles were evaluated for their anti-inflammatory and antioxidant properties.

Keywords: α-β-Dibromochalcones, 1,3,5-Trisubstituted pyrazoles, Tetrabutylammonium tribromide, Anti-inflammatory and antioxidant activities

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INTRODUCTION

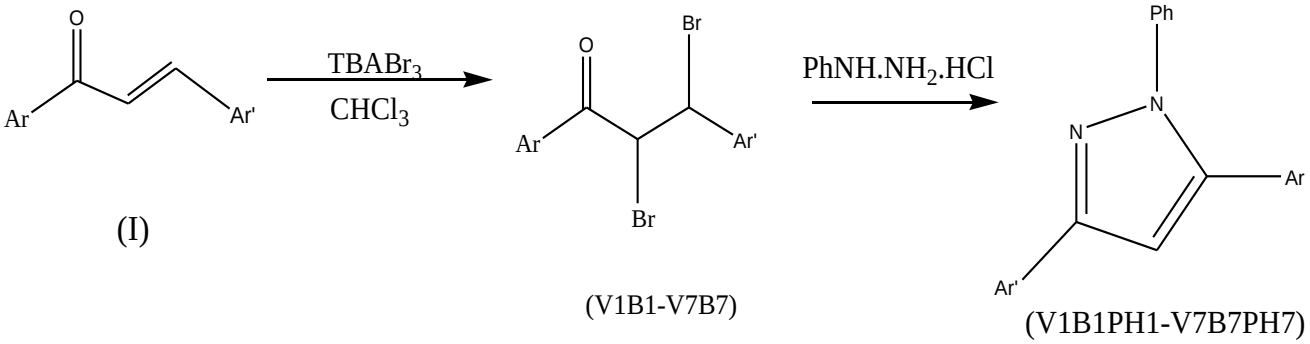
Pyrazoles are one of the most valuable heterocycles as they are potential bioactive agents due to their wide spectrum of pharmacological activities like anti-inflammatory, antimicrobial, calcium channel blockers, antihypertensive, analgesic, antitumor, antiviral, antibacterial, anticancer, antimalarial, antitubercular, hypoglycemic etc.[1-4] Pyrazoles are also useful as catalysts[5] ,ligands[6] or as moieties to increase regio- and stereoselectivity[7] and as an intermediates for the synthesis of various fused pyrazoles[8]. Chalcones act as a fine reactant for the synthesis of various different heterocyclic rings. Pyrazoles derived from chalcones are of great interest because of their different biological and pharmacological properties. α-β-Dibromochalcones are active intermediates in the synthesis of biologically active cyclic compounds like pyrazoles, pyrazolines and isoxazoles etc. They have served as valuable substrates to bring about a variety of chemical reactions.[9-15]

In view of the above facts, the present study encourages the synthesis of 1,3,5-trisubstituted pyrazole derivatives from α-β-Dibromochalcones which can be prepared by using bromine or N-bromosuccinimide in the weakly polar aprotic solvents like CCl_4, $CHCl_3$, CH_2Cl_2 but yields are very limited.[16,17] So, the use of tetrabutylammonium tribromide ($TBABr_3$) causes regioselective bromination of chalcones and gives high yield without polymerization. $TBABr_3$ is easy to use under mild conditions and unlike bromine it is neither corrosive nor toxic. It is prepared by the addition of hydrobromic acid to an aqueous solution of tetrabutyl ammonium bromide and sodium bromide at room temperature.[18]

RESULTS AND DISCUSSION

Synthesis

Various derivatives of α-β-Dibromochalcones were prepared by the reaction of different chalcones (I) with tetrabutylammonium tribromide ($TBABr_3$). These α-β-Dibromochalcones (V1B1-V7B7) were treated with phenylhydrazine hydrochloride to give different 1,3,5-trisubstituted pyrazoles (V1B1PH1-V7B7PH7)(Scheme 1).Physical data of the synthesized compounds are given in the Table 1& 2.The reaction gave single colorless product and a good yield in the range 65-72%. The compounds were purified by recrystallization from ethanol and dried under vacuum. The synthesized compounds were characterized by IR, ^{1}NMR and elemental analysis.



(I) (V1B1-V7B7) (V1B1PH1-V7B7PH7)

Scheme 1: Synthetic sequence of α-β chalcone dibromides and 1,3,5 trisubstituted Pyrazole

Table 1: Physical data of α-β-Dibromochalcones

Sr No.	Compound	Ar	Ar'	Melting Point(^{0}C)	Yield (%)
1	V1B1	$C_{10}H_7$	C_6H_5	104-106	76
2	V2B2	$C_{10}H_7$	4-ClC_6H_4	108-110	75
3	V3B3	$C_{10}H_7$	4-$NO_2C_6H_4$	94-96	68
4	V4B4	$C_{10}H_7$	4-$MeOC_6H_4$	121-123	63
5	V5B5	$C_{10}H_7$	4-FC_6H_4	145-147	70
6	V6B6	$C_{10}H_7$	4-MeC_6H_4	132-134	66
7	V7B7	$C_{10}H_7$	4-OHC_6H_4	118-120	69

Table 2: Physical data of 1,3,5 trisubstituted pyrazoles

Sr No.	Compound	Ar	Ar'	Melting Point(^{0}C)	Yield (%)
1	V1B1PH1	$C_{10}H_7$	C_6H_5	112-114	65
2	V2B2PH2	$C_{10}H_7$	4-ClC_6H_4	102-104	69
3	V3B3PH3	$C_{10}H_7$	4-$NO_2C_6H_4$	110-112	72
4	V4B4PH4	$C_{10}H_7$	4-$MeOC_6H_4$	126-128	73
5	V5B5PH5	$C_{10}H_7$	4-FC_6H_4	105-107	69
6	V6B6PH6	$C_{10}H_7$	4-MeC_6H_4	116-117	72
7	V7B7PH7	$C_{10}H_7$	4-OHC_6H_4	130-132	70

Biological Evaluation

In Vitro Antioxidant Activity

DPPH (1,1-diphenyl-2-picrylhydrazyl) free radical scavenging method was used for the determination of antioxidant activity. The test compound was mixed with 95% methanol to make a stock solution of concentration 100µg/ml. From stock solution different solutions of concentration 10µg/ml, 20µg/ml, 40µg/ml, 60µg/ml and 100µg/ml were prepared. Ascorbic acid was used as a standard and different concentrations of the standard were prepared as that of the test compound. The reaction mixture containing 1ml of 0.3mmol DPPH methanol solution was added to 2.5ml of sample solution of different concentrations and allowed to react at room temperature. After 15min. incubation period at 37^{0}C absorbance was calculated at 517nm. Control reading was observed without the test compound.

% scavenging = [(Absorbance of control- Absorbance of test compound)/ (Absorbance of control)] X 100

The free radical scavenging activity of the synthesized compounds were evaluated through the ability of the compounds to quench the DPPH using ascorbic acid as a standard.

The results are given in the **table 3**. All the synthesized compounds were less potent than the standard. The compounds **V5B5PH5** and **V7B7PH7** exhibited moderate antioxidant activity in comparison to the standard.

Table 3: Antioxidant activity of the 1,3,5 trisubstituted Pyrazoles by using DPPH free radical scavenging method

Sr. No.	Compound	% Inhibition					Antioxidant IC50 value
		10µg/ml	20µg/ml	40µg/ml	60µg/ml	100µg/ml	
1	V1B1PH1	2.48	6.89	18.88	26.34	33.78	137.67
2	V2B2PH2	1.25	8.98	12.55	19.98	22.35	213.37
3	V3B3PH3	2.88	3.04	13.80	18.65	24.09	194.29
4	V4B4PH4	24.8	31.98	37.63	43.66	51.76	88.45
5	V5B5PH5	27.7	39.32	45.77	53.98	65.34	63.49
6	V6B6PH6	8.73	12.12	22.57	31.09	38.98	125.00
7	V7B7PH7	22.65	33.73	46.89	53.92	63.23	59.92
8	Ascorbic acid(Standard)	48.01	69.94	78.76	89.32	94.56	11.20

***In Vivo* Anti-Inflammatory Activity**

The anti-inflammatory activities of the compounds were determined by using Carrageenan induced paw edema method. Adult male rats (≈ 250g) were used to evaluate anti-inflammatory activity. Ten groups were made each having six animals. The different groups of rats were pre-treated with their respective doses. After 1 hour, oedema was induced by administration of 0.1 ml of 1% carrageenan suspension into sub-plantar region of left hind paw of each rat and paw volume was measured by using Plethysmometer (Laboratory enterprises, Nasik), at 0, 1, 2, 3, 4 hr interval. Mean ± SEM for treated and control animals is calculated and compared for each time interval and were statistically analyzed.

Group I: Normal control

Group II: Inflammation control group received vehicle (0.25% Carboxymethylcellulose).

Group III: Standard group treated with Diclofenac sodium (100 mg/kg *p.o.*)

Group IV: Inflammation + V1B1PH1 (100 mg/kg *p.o.*)

Group V: Inflammation + V2B2PH2 (100 mg/kg *p.o.*)

Group VI: Inflammation + V3B3PH3 (100 mg/kg *p.o.*)

Group VII: Inflammation + V4B4PH4 (100 mg/kg *p.o.*)

Group VIII: Inflammation + V5B5PH5 (100 mg/kg *p.o.*)

Group IX: Inflammation + V6B6PH6 (100 mg/kg *p.o.*)

Group X: Inflammation + V7B7PH7 (100 mg/kg *p.o.*)

Diclofenac sodium was used as a standard drug. The adult male rats were fasted overnight with free access to water. The standard drug was taken in the concentration of 20mg/kg. The synthesized compounds were given at the dose of 150mg/kg and were administered via oral route. A 1% suspension of carrageenan was prepared in saline. 0.05ml of this suspension was injected into the planter tissue of left hind paw to induce edema. For control the animals were injected with equal volumes of saline and the paw volume of rats was measured. Results are given in the **table 4**. The compounds**V4B4PH4** and **V7B7PH7** show remarkable anti-inflammatory activity.

Table 4: Anti-inflammatory activity of 1,3,5-trisubstituted Pyrazole derivatives

Treatment group	Paw volume (mm) after time (hrs)				
	0 hr	1 hr	2hr	3hr	4hr
V1B1PH1	0.92±0.049	1.16±0.080	1.20±0.067	1.27±0.046	1.29±0.024
V2B2PH2	0.96±0.095	1.18±0.071	1.26±0.051	1.30±0.035	1.36±0.078
V3B3PH3	0.99±0.038	1.19±0.077	1.28±0.037	1.32±0.015	1.38±0.039
V4B4PH4	0.66±0.045	0.72±0.034	0.80±0.031	0.82±0.021	0.88±0.045
V5B5PH5	0.90±0.084	1.12±0.065	1.22±0.052	1.28±0.039	1.36±0.047
V6B6PH6	0.86±0.022	1.05±0.047	1.12±0.050	1.22±0.056	1.26±0.030
V7B7PH7	0.90±0.067	1.04±0.036	1.06±0.081	1.12±0.062	1.14±0.083
CONTROL	0.80±0.026	0.81±0.025	0.82±0.017	0.82±0.019	0.81±0.023
Infalmmatory Control	0.96±0.028	1.14±0.066	1.24±0.043	1.30±0.042	1.38±0.054
Diclofenac	0.86±0.012	0.96±0.012	0.92±0.012	0.84±0.019	0.82±0.016

Values are expressed as mean ± SEM (standard error mean)
Values are calculated as compared to control using one way ANOVA followed by Dunnet's test

Experimental Section

Melting points of the synthesized compounds were determined by open capillary method and were uncorrected. TLC was done to check the purity and to monitor the reaction. The IR spectra were recorded on Shimadzu FTIR 8400 spectrophotometer using potassium bromide pallet. ^{1}HNMR spectra were obtained in $CDCl_3$ on a Bruker Spectrometer at 400 Hz. The chemical shifts are reported in ppm (δ) in relation to Tetramethylsilane (TMS) as an internal standard. Coupling constants (J) are expressed in Hertz (Hz). All the chemicals and reagents used were procured from Merck and Sigma Aldrich.

Synthesis

1) General procedure for the synthesis of α-β-Dibromochalcones from chalcones

Chalcone (0.005mmol) and tetrabutylammonium tribromide ($TBABr_3$) (0.005mmol) were dissolved in 100ml of chloroform. The reaction mixture was sonicated at room temperature until discoloration of the solution (red colored to yellowish to colorless) took place. Completion of the reaction was confirmed by TLC using diethyl ether-hexane (20:80) as mobile phase. The solvent was evaporated and the residue was dissolved in diethyl ether, washed with aqueous 5% sodium thiosulphate solution and water. Final product was precipitated out by the addition of small amount of ethanol. **(V1B1-V7B7)**

1.1. 2,3-dibromo-1-(naphthalene-6-yl)-3-phenylpropan-1-one (V1B1)

IR (νmax, in KBr): 1678 cm^{-1} (CO stretch); ^{1}H NMR ($CDCl_3$, 300 MHz, δ): 5.73 (d, 1H(α), CH, J = 8.1 Hz); 5.66 (d, 1H(β), CH, J = 8.1 Hz); 7.12-7.14 (m, 2H, ArH); 7.08-7.21 (m, 3H, ArH); 7.42-8.31(m,7H,ArH); Elemental analysis: Calculated for $C_{20}H_7Br_2O$; C 55.46, H 3.96 Found C 56.76, H 1.67

1.2. 2,3-dibromo-3-(4-Chlorophenyl)-1-(naphthalene-6-yl)propan-1-one (V2B2)

IR (νmax, in KBr): 1680 cm^{-1} (CO stretch); ^{1}H NMR ($CDCl_3$, 300 MHz, δ): 5.55 (d, 1H(α), CH, J = 8.1 Hz); 5.45 (d, 1H(β), CH, J = 8.1 Hz); 7.31 (d, 2H, ArH, J = 8.4 Hz); 7.53 (d, 2H, ArH, J = 8.4 Hz); 7.41-8.29 (m,7H,ArH); Elemental analysis: Calculated for $C_{20}H_{16}Br_2OCl$; C 51.37, H 3.45 Found C 51.35, H 3.40

1.3. 2,3-dibromo-1-(naphthalene-6-yl)-3-(4-nitrophenyl)propan-1-one (V3B3)

IR (νmax, in KBr): 1674 cm^{-1} (CO stretch) ;^{1}H NMR ($CDCl_3$, 300 MHz, δ): 5.73 (d, 1H, CH, J = 8.1 Hz); 5.66 (d, 1H, CH, J = 8.1 Hz); 7.38 (d, 2H, ArH, J = 8.4 Hz); 8.14 (d, 2H, ArH, J = 8.4

Hz); 7.43-8.31 (m,7H,ArH); Elemental analysis: Calculated for $C_{20}H_{16}Br_2NO_3$; C 50.24, H 3.37 Found C 50.22, H 3.35

1.4. 2,3-dibromo-3-(4-methoxyphenyl)-1-(naphthalene-6-yl)propan-1-one (V4B4)

IR (νmax, in KBr): 1680 cm^{-1} (CO stretch); ^1H NMR ($CDCl_3$, 300 MHz, δ): 3.73 (s, 3H, OCH_3); 5.72 (d, 1H(α), CH, J = 8.1 Hz); 5.60 (d, 1H(β), CH, J = 8.1 Hz); 6.72-7.01 (m, 4H, ArH); 7.39-8.296 (m,7H,ArH); Elemental analysis: Calculated for $C_{21}H_{19}Br_2O_2$; C 54.45, H 4.13 Found C 54.43, H 4.14

1.5. 2,3-dibromo-3-(4-fluorophenyl)-1-(naphthalene-6-yl)propan-1-one (V5B5)

IR (νmax, in KBr): 1674 cm^{-1} (CO stretch); ^1H NMR ($CDCl_3$, 300 MHz, δ): 5.55 (d, 1H(α), CH, J = 8.1 Hz); 5.45 (d, 1H(β), CH, J = 8.1 Hz); 7.30 (d, 2H, ArH, J = 8.4 Hz); 7.55 (d, 2H, ArH, J = 8.4 Hz); 7.39-8.28 (m,7H,ArH); Elemental analysis: Calculated for $C_{20}H_{16}Br_2OF$; C 53.25, H 3.57 Found C 53.22, H 3.58

1.6. 2,3-dibromo-1-(naphthalene-6-yl)-3-*p*-tolyl-propan-1-one (V6B6)

IR (νmax, in KBr): 1681 cm^{-1} (CO stretch)

^1H NMR ($CDCl_3$, 300 MHz, δ): 2.35 (s, 3H, CH_3); 5.73 (d, 1H(α), CH, J = 8.1 Hz); 5.66 (d, 1H(β), CH, J = 8.1 Hz); 7.17-7.27 (m, 4H, ArH); 7.40-8.32 (m,7H,ArH); Elemental analysis: Calculated for $C_{21}H_{19}Br_2O$; C 56.40, H 4.28 Found C 56.38, H 4.27

1.7. 2,3-dibromo-3-(4-hydroxyphenyl)-1-(naphthalene-6-yl)propan-1-one (V7B7)

IR (νmax, in KBr): 1674 cm^{-1} (CO stretch); ^1H NMR ($CDCl_3$, 300 MHz, δ): 5.55 (d, 1H(α), CH, J = 8.1 Hz); 5.45 (d, 1H(β), CH, J = 8.1 Hz); 7.31 (d, 2H, ArH, J = 8.4 Hz); 7.53 (d, 2H, ArH, J = 8.4 Hz); 7.42-8.30 (m,7H,ArH); 6.68-6.95 (m, 4H, ArH); 5.00 (s, 1H,OH); Elemental analysis: Calculated for $C_{21}H_{20}O_2Br_2$; C 54.34, H 4.34 Found C 54.32, H 4.32

2. General procedure for the synthesis of 1,3,5 trisubstituted Pyrazoles from α-β chalcone dibromides

A mixture of chalcone dibromide (0.556 g, 0.001mol) and phenylhydrazine hydrochloride (0.162 g, 0.0015mol) in ethanol was refluxed for about 3 hrs. The mixture was poured onto ice-cold water. Resulting mixture was then extracted with dichloromethane in three portions (3 × 50 ml). The organic extract was dried over anhydrous sodium sulphate and filtered. Dichloromethane was evaporated in vacuum to give the crude product, which was purified by column chromatography on silica gel (100-200 mesh) by using pet ether-ethyl acetate as an eluent to give pure pyrazoles **(V1B1PH1-V7B7PH7)**.

2.1 5-(naphthalen-1-yl)-1,3-diphenyl-1*H*-pyrazole (V1B1PH1)

IR (νmax, in KBr): Peak absent in CO region; ^1H NMR ($CDCl_3$, 300 MHz, δ): 7.25-7.34 (m, 4H, ArH); 7.68 (s, 1H, C_3-pyrazole proton); 7.23-7.33 (m, 10H, ArH); 6.60-6.98 (m,7H,ArH); Elemental analysis: Calculated for $C_{25}H_{18}N_2$; C 86.68, H 5.24 Found C 86.67, H 5.24

2.2 3-(4-Chlorophenyl)-5-(naphthalen-1-yl)-1phenyl-1*H*-pyrazole (V2B2PH2)

IR (νmax, in KBr): Peak absent in CO region; ^1H NMR ($CDCl_3$, 300 MHz, δ): 7.03 (d, 2H, ArH, J = 8.1 Hz); 7.23 (d, 2H, ArH, J = 8.1 Hz); 7.29-7.35 (m, 5H, ArH); 7.81 (s, 1H, C_3- pyrazole proton); 6.60-6.98 (m,7H,ArH); Elemental analysis: Calculated for $C_{25}H_{17}N_2Cl$; C 78.84, H 4.50 Found C 78.82, H 4.50

2.3 5-(naphthalen-1-yl)- 3-(4-Nitrophenyl)-1-phenyl-1*H*-pyrazole (V3B3PH3)

IR (νmax, in KBr): Peak absent in CO region; ^1H NMR ($CDCl_3$, 300 MHz, δ): 6.89 (d, 2H, ArH, J = 8.1 Hz); 7.21 (d, 2H, ArH, J = 8.1 Hz); 7.18-7.25 (m, 5H, ArH); 7.68 (s, 1H, C_3- pyrazole proton); 6.58-6.81 (m,7H,ArH); Elemental analysis: Calculated for $C_{25}H_{17}N_3O_2$; C76.71, H 4.38 Found C 76.70, H 4.38

2.4 3-(4-methoxyphenyl)-5-(naphthalen-1-yl)-1phenyl-1*H*-pyrazole V4B4PH4)

IR (νmax, in KBr): Peak absent in CO region; ^1H NMR ($CDCl_3$, 300 MHz, δ): 6.91 (d, 2H, ArH, J = 8.1 Hz); 7.26 (d, 2H, ArH, J = 8.1 Hz); 7.29-7.35 (m, 5H, ArH); 7.67 (s, 1H, C_3- pyrazole proton); 6.60-6.98 (m,7H,ArH); 3.81 (s, 3H, OCH_3); Elemental analysis: Calculated for $C_{26}H_{20}N_2O$; C 82.95, H 5.35 Found C 82.94, H 5.36

2.5 3-(4-fluorophenyl)-5-(naphthalen-1-yl)-1phenyl-1*H*-pyrazole (V5B5PH5)

IR (νmax, in KBr): Peak absent in CO region; ^1H NMR ($CDCl_3$, 300 MHz, δ): 7.02 (d, 2H, ArH, J = 8.1 Hz); 7.21 (d, 2H, ArH, J = 8.1 Hz); 7.19-7.25 (m, 5H, ArH); 7.79 (s, 1H, C_3- pyrazole proton); 6.58-6.89 (m,7H,ArH); Elemental analysis: Calculated for $C_{25}H_{17}FN_2$; C 82.40, H 4.70 Found C 82.39, H 4.71

2.6 5-(naphthalen-1-yl)-1phenyl-3-*p*-tolyl-1*H*-pyrazole (V6B6PH6)

IR (νmax, in KBr): Peak absent in CO region; ^1H NMR ($CDCl_3$, 300 MHz, δ): 7.14 (d, 2H, ArH, J = 8.1 Hz); 7.26 (d, 2H, ArH, J = 8.1 Hz); 7.49-7.58 (m, 5H, ArH); 7.69 (s, 1H, C_3- pyrazole proton); 6.60-6.98 (m,7H,ArH); 2.33 (s, 3H, CH_3); Elemental analysis: Calculated for $C_{26}H_{20}N_2$; C 86.64, H 5.59 Found C 86.63, H 5.60

2.7 4-(5-(naphthalen-1-yl)-1-phenyl-1*H*-pyrazole-3-yl) phenol (V7B7PH7)

IR (νmax, in KBr): Peak absent in CO region; ^1H NMR ($CDCl_3$, 300 MHz, δ): 7.02 (d, 2H, ArH, J = 8.1 Hz); 7.13 (d, 2H, ArH, J = 8.1 Hz); 7.39-7.65 (m, 5H, ArH); 7.75 (s, 1H, C_3- pyrazole proton); 6.54-6.87 (m,7H,ArH); Elemental analysis: Calculated for $C_{25}H_{18}N_2O$; C 82.85, H 5.01 Found C 82.84, H 5.01

CONCLUSION

Different 1,3,5-trisubstituted pyrazoles were synthesized from chalcone dibromides and were characterized by IR, NMR and elemental analysis. Evaluation for antioxidant property was done by using DPPH free radical scavenging activity. The compounds **V5B5PH5** and **V7B7PH7** exhibited moderate antioxidant activity when compared with the standard. *In vivo* anti-inflammatory activity of these compounds showed that **V4D4PH4** and **V7D7PH7** possess good activity than the standard.

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