DOI: 10.22607/IJACS.2017.501006

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Indian
Journal of Advances in
Chemical Science

Indian Journal of Advances in Chemical Science 5(1) (2017) 43-49

Synthesis, Antimicrobial, and Antioxidant Activities of Some Novel Flavones and Pyrazolines Derived from Chalcones

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Received 24th December 2016; Revised 03rd January 2017; Accepted 09th January 2017

ABSTRACT

In this work, synthesis of four novel flavones (2a-d) and four pyrazoline derivatives (3a-d) have been described. 2-hydroxy chalcones (1a-d) underwent oxidative cyclization with I_2-dimethyl sulfoxide to afford 2a-d, whereas condensation cyclization of the same chalcones with hydrazine hydrate in ethanol yielded 3a-d. Chalcones required were synthesized by Claisen-Schmidt condensation of substituted 2- hydroxy acetophenones (a-d) and benzyloxy benzaldehyde (1). The structures of the title compounds 2a and 3a were characterized by chemical reactions, elemental analysis, and spectral methods such as IR, ^1H NMR and mass spectra. The synthesized compounds were evaluated for in-vitro antibacterial and antioxidant activities against standard. The zone of inhibition for some of the newly synthesized compounds showed notable antibacterial activity against selected bacterial strains compared with chloramphenicol. Significant antioxidant activities were also shown by flavones and pyrazolines.

Key words: *Flavones, Pyrazolines, Benzyloxy benzaldehyde, Chalcones, Antibacterial antioxidant.*

1. INTRODUCTION

Flavones are a class of flavonoids based on the backbone of 2-phenylchromen-4-one [1]. Natural flavones include apigenin, luteolin, tangeritin, chrysin, baicalein, scutellarein, and wogonin. Synthetic flavones include diosmin, flavoxate, and 7,8-dihydroxyflavone. Flavones have effects on CYP (P450) activity [2,3] which are enzymes that metabolize most drugs in the body.

Similarly, among nitrogen containing five membered heterocycles, pyrazoline is a dihydropyrazole and π-excessive aromatic monocyclic heterocycle containing two nitrogen atoms with only one endocyclic double bond in a five member ring. Pyrazolines have attracted attention of medicinal chemists for both with regard to heterocyclic chemistry and the pharmacological activities associated with them.

Reviews available in the literature suggest several methods exist for the synthesis of flavones [4,5] and pyrazolines [6-12]. In 1967, Jacobe reviewed the chemistry of pyrazolines, which have been studied extensively for their biodynamic behavior [13] and industrial applications [14]. Pyrazoline has been reported to acquire antimicrobial [15], antibacterial [16-18], antifungal [19-21], antidiabetic [22], antitubercular [23], antidiuretic [24], and antianalgesic [25]. Among the biological activities displayed by flavonoids antimalarial [26], antidepressant [27], and antihypolipemic activities [28] are prominent. Flavones and pyrazolines possessing interesting biological activities have stimulated considerable research work in recent years leading to the synthetic utility of the derivatives of this ring system.

In our search for new potential antimicrobial compounds, inspection of the research work and in view of importance of flavones and pyrazolines, it was anticipated to plan for synthesizing them. Claisen-Schmidt condensation of different aromatic ketones and benzyloxy benzaldehyde yielded chalcones [29]. The reaction of chalcones with I_2/dimethyl sulfoxide (DMSO) was utilized for synthesizing flavones whereas in continuation to our research work [30] we found it interesting to treat these chalcones with hydrazine hydrate in ethanol to afford some novel pyrazoline derivatives. Simultaneously, we thought to evaluate their antibacterial and antioxidant activities.

2. EXPERIMENTAL

2.1. Material and Methods

All AR grade chemicals of Merck, S.D. Fine and Aldrich were used for the synthesis without further

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purification. The melting points were recorded in open capillary in paraffin bath and are uncorrected. IR spectra were recorded on a Shimadzu IR spectrophotometer (KBr, v max in cm^{-1}). ^1H NMR spectra are recorded on a Bruker AM 400 instrument (400 MHz) using tetramethylsilane as an internal reference and DMSO-d_6 as solvent. Chemical Shifts are given in parts per million (ppm). Positive-ion electro spray ionization mass spectra were obtained with a Waters Micromass Q-TOF micro, mass spectrophotometer. Elemental (CHN) analysis was done using thermo scientific (Flash-2000), the compounds were analyzed for carbon, hydrogen, and nitrogen and the results obtained are in good agreement with the calculated values. The reactions were monitored by E. Merck TLC aluminum sheet silica $gel_{60}F_{254}$ and visualizing the spot in UV cabinet and iodine chamber. Starting compounds such as 2- hydroxy acetophenones (a-d) and benzyloxy benzaldehyde (1) were synthesized by adopting the procedure published in the literature [31].

2.2. General Procedure for the Synthesis of 3-[4-(benzyloxy)phenyl]-1-(5-substituted-2-hydroxyphenyl)prop-2-en-1-one (1a-d) [29]

a-d (10 mmol) was dissolved in minimum quantity of ethanol. Benzyloxy benzaldehyde (1, 10 mmol) was added to above solution and the solution was heated till the solid get dissolved. Aqueous 70% sodium hydroxide solution (10 mL) was added drop wise with constant stirring. The mixture was further stirred mechanically at room temperature to obtain dark orange mass. The reaction mixture was kept overnight and then acidified by 1:1 hydrochloric acid. The solid obtained was filtered, washed with water, and recrystallized from glacial acetic acid to yield 1a-d (Reaction scheme 1).

2.2.1. 3-(4-(benzyloxy)phenyl)-1-(5-bromo-2-hydroxyphenyl)prop-2-en-1-one (1a)

Orange colored crystals; MP: 142-144°C; yield 70%; IR(KBr, ν_{max}): 3461 (−OH), 3036 (ArH), 2875, 2937 (CH_2), 1634 (C=O), 1556, 1508 (C=C) cm^{-1}; ^1H NMR (DMSO-d_6): δ 12.65 (s,1H, −OH), 5.19 (s,2H, $-CH_2$), 6.94-8.40 (m, 14H, ArH; −CH=CH−) ppm; MS: m/z (%) 411 $[M+2]^+$, 412 $[M+3]^+$; M. F. $C_{22}H_{17}O_3Br$; calculated: C, 64.71; H, 4.16; found: C, 63.008; H, 4.136.

2.2.2. 3-(4-(benzyloxy)phenyl)-1-(5-chloro-2-hydroxyphenyl)prop-2-en-1-one (1b)

Orange colored crystals; MP: 131-133°C; yield 60%; M. F. $C_{22}H_{17}O_3Cl$.

2.2.3. 3-(4-(benzyloxy)phenyl)-1-(5-methyl-2-hydroxyphenyl)prop-2-en-1-one (1c)

Orange colored crystals; MP: 134-136°C; yield 68%; M. F. $C_{23}H_{20}O_3$.

2.2.4. 3-(4-(benzyloxy)phenyl)-1-(3,5-dichloro-2-hydroxyphenyl)prop-2-en-1-one (1d)

Orange colored crystals; MP: 162-164°C; yield 77%; M. F. $C_{22}H_{17}O_3Cl_2$.

2.3. General Procedure for the Synthesis of 2-[4-(benzyloxy)phenyl]-6-substituted-4H-chromen-4-one (2a-d)

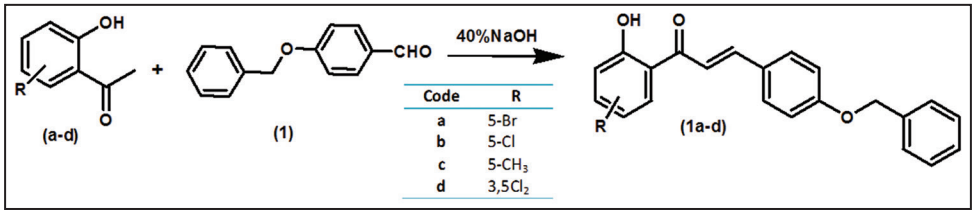
Chalcones 1a-d (3.676 mmol) was dissolved in DMSO (45 mL) and iodine crystals (0.024 g) were then added. The reaction mixture was stirred and refluxed at 130-140°C in an oil bath for 2 h. The contents were cooled and poured into crushed ice, filtered, washed with saturated solution of sodium thiosulfate and water and then dried. The crude product was recrystallized from ethanol to get 2a-d (Reaction Scheme 2).

2.3.1. 2-[4-(benzyloxy)phenyl]-6-bromo-4H-chromen-4-one (2a)

Pale yellow crystals; MP: 182-184°C; yield 73.42%; Rf=0.73; IR(KBr, ν_{max}): 3065, 3031 (ArH), 2849, 2866, 2917 ($-CH_2$), 1632 (C=O), 1574, 1561, 1511 (C=C), 1123,1140 (C-O-C), 769 (C-Br) cm^{-1}; ^1H NMR (DMSO-d_6): δ 5.22 (s,2H, $-CH_2$), 6.95-8.2349 (m, 13H, ArH) ppm; MS: m/z 408 $[M+H]^+$, 430 $[M+Na]^+$; M. F. $C_{22}H_{15}O_3Br$; calculated: C, 64.88; H, 3.71; found: C, 65.01; H, 3.62.

2.3.2. 2-[4-(benzyloxy)phenyl]-6-chloro-4H-chromen-4-one (2b)

Pale yellow crystals; MP: 191-192°C; yield 63.69%; Rf=0.65; IR(KBr, ν_{max}): 3060, 3024 (ArH), 2886, 2934 ($-CH_2$), 1630 (C=O), 1570, 1557 (C=C), 1127, 1144 (C-O-C) cm^{-1}; M. F. $C_{22}H_{15}O_3Cl$; calculated: C, 72.83; H, 4.71; found: C, 72.92; H, 4.54.



Scheme 1: Synthesis of 2-hydroxy chalcones (1a-d).

2.3.3. 2-[4-(benzyloxy)phenyl]-6-methyl-4H-chromen-4-one (2c)

Pale yellow crystals; MP: 210-211°C; yield 64.6%; Rf=0.81; IR(KBr, ν_{max}): 3042, 3010 (ArH), 2817, 2942 (−CH_2, −CH_3), 1627 (C=O), 1510, 1435 (C=C), 1128 (C-O-C) cm^{-1}; M. F. $C_{23}H_{18}O_3$; calculated: C, 80.68; H, 5.30; found: C, 80.70; H, 5.23.

2.3.4. 2-[4-(benzyloxy)phenyl]-6,8-dichloro-4H-chromen-4-one (2d)

Pale yellow crystals; MP: 152-153°C; yield 72%; Rf=0.66; IR(KBr, ν_{max}): 3072, 3030 (ArH), 2878, 2951 (−CH_2), 1638 (C=O), 1572, 1462 (C=C), 1128,1141 (C-O-C), cm^{-1}; M. F. $C_{22}H_{14}O_3Cl_2$; calculated: C, 66.52; H, 3.55; found: C, 67.09; H, 3.52.

2.4. General Procedure for the Synthesis of 2-{5-[4-(benzyloxy)phenyl]-4,5-dihydro-1H-pyrazol-3-yl}-4-substituted phenol (3a-d)

Chalcones 1a-d (2.45 mmol) was dissolved in ethanol (20 mL), then hydrazine hydrate (1 mL) was added; reaction mixture was refluxed for 2 h, cooled, product obtained was filtered, washed, and recrystallized from ethanol to get 3a-d (Reaction Scheme 2).

2.4.1. 2-{5-[4-(benzyloxy)phenyl]-4,5-dihydro-1H-pyrazol-3-yl}-4-bromophenol (3a)

White shiny crystals; MP: 124-126°C; yield 67.8%; Rf=0.77; IR(KBr, ν_{max}): 3451 (-OH), 3307 (−NH), 3034, (ArH), 2871, 2917 (−CH_2), 1647, 1587 (C=N), 1060, 1082 (C-O-C), cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.95-3.02 (dd, J=9.33Hz, 1H, −CH_A), 3.51-3.57(dd, J=8Hz, 1H, −CH_A), 4.79-4.84 (dd, J=10.0Hz, 1H, −CH_A), 5.08 (s,2H, −CH_2), 6.85-7.39 (m, 12H, ArH), 11.23 (s,1H, −OH), 8.26 (s,1H, −NH) ppm; MS: m/z (%) 423 $[M]^+$, 425$[M+2]^+$; M. F. $C_{22}H_{19}O_2N_2Br$; calculated: C, 62.56; H, 4.50; N, 6.63. Found: C, 62.23; H, 4.90; N, 5.79.

2.4.2. 2-{5-[4-(benzyloxy)phenyl]-4,5-dihydro-1H-pyrazol-3-yl}-4-chlorophenol (3b)

White shiny crystals; MP: 118-119°C; yield 69%; Rf=0.88; IR(KBr, ν_{max}): 3415 (−OH), 3315 (−NH), 3034 (ArH), 2865, 2922 (−CH_2), 1515 (C=N), 1457 (C=C), 1061 (C-O-C), cm^{-1}; M. F. $C_{22}H_{19}O_2N_2Cl$; calculated: C, 69.75; H, 5.05; N, 7.39. Found: C, 70.01; H, 4.98; N, 7.18.

2.4.3. 2-{5-[4-(benzyloxy)phenyl]-4,5-dihydro-1H-pyrazol-3-yl}-4-methylphenol (3c)

White shiny crystals; MP: 106-108°C; yield 78%; Rf=0.74; IR(KBr, ν_{max}): 3423 (−OH), 3307 (−NH), 3034 (ArH), 2868, 2942 (−CH_2, −CH_3), 1588 (C=N), 1415 (C=C), 1067, 1048 (C-O-C), cm^{-1}; M. F. $C_{23}H_{22}O_2N_2$; calculated: C, 77.07; H, 6.19; N, 7.82. Found: C, 76.98; H, 6.15; N, 7.80.

2.4.4. 2-{5-[4-(benzyloxy)phenyl]-4,5-dihydro-1H-pyrazol-3-yl}-4,6-dichlorophenol (3d)

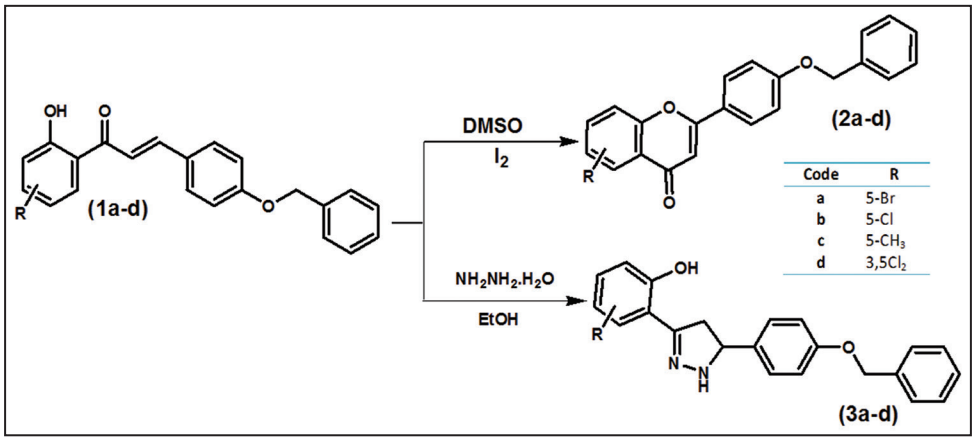
White shiny crystals; MP: 137-139°C; yield 82%; Rf=0.87; IR(KBr, ν_{max}): 3450 (−OH), 3322 (−NH), 3030 (ArH), 2859 (−CH_2), 1575 (C=N), 1417 (C=C), 1061 (C-O-C), cm^{-1}; M.F. $C_{22}H_{18}O_2N_2Cl_2$; calculated: C, 63.93; H, 4.39; N, 6.78. Found: C, 63.75; H, 4.36; N, 6.79.

2.5. Antibacterial Activity

The novel synthesized heterocyclic compounds were screened for their *in-vitro* antimicrobial activity using cup plate Agar disc-diffusion method against two Gram-positive bacterial strains, *Bacillus thuringiensis* and *Staphylococcus aureus* and two Gram-negative strains, *Escherichia coli* and *Enterobacter aerogenes* against chloramphenicol as standard.

2.5.1. General procedure for the determination of zone of inhibition by Agar disc-diffusion method

Test solutions were prepared with known weight of compound in dimethyl sulfoxide (DMSO) and diluted suitably to give the resultant concentration of 31, 62, 125, 250, and 500 µg/mL. Whatman no. 1 sterile filter paper discs (6 mm) were impregnated with solution and allowed to dry at room temperature. *In-vitro* antibacterial activity was determined using Mueller Hinton Agar obtained from Himedia Ltd., Mumbai.



Scheme 2: Synthesis of Flavones (2a-d) and Pyrazolines (3a-d).

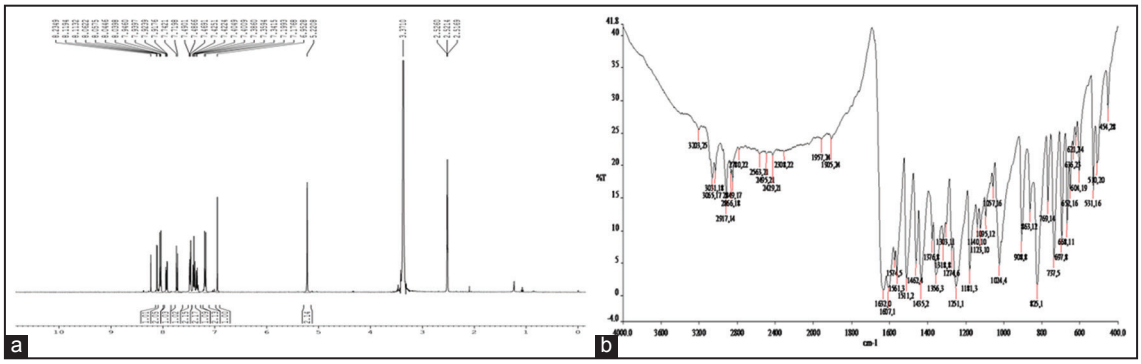


Figure 1: Spectra of 2-[4-(benzyloxy)phenyl]-6-bromo-4H-chromen-4-one (2a): (a) NMR spectrum, (b) Fourier transform infrared spectroscopy spectrum.

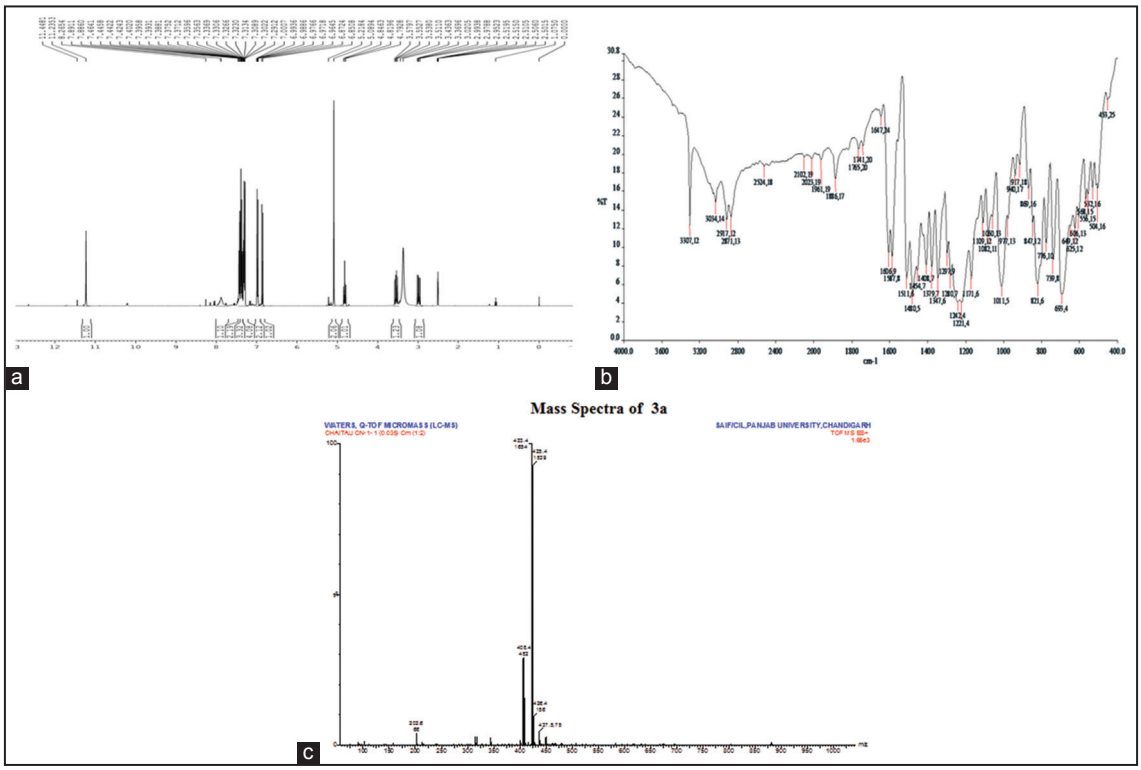


Figure 2: Spectra of 2-{5-[4-(benzyloxy)phenyl]-4,5-dihydro-1H-pyrazol-3-yl}-4-bromophenol (3a): (a) NMR spectrum, (b) Fourier transform infrared spectroscopy spectrum, (c) Mass spectrum.

24 h old culture of selected bacterial strain was mixed with physiological saline and the turbidity was corrected by adding sterile physiological saline and sub cultured on Sabouraud Dextrose and suspended in sterile distilled water to an absorbance of 0.6 at 450 nm. Petri plates were prepared by pouring 10 mL of Mueller Hinton Agar for bacteria containing microbial culture was allowed to solidify. The discs were then applied, and the plates were incubated at 37°C for 24 h (bacteria) and the inhibition zone was measured as diameter in four directions and expressed as mean. The results were compared using chloramphenicol as a standard antibacterial agent. The results of antibacterial activity (i.e., Zone of inhibition in mm) are given in the Table 1.

2.6. Antioxidant Activity

2.6.1. Reducing power

The reducing power [32] *in-vitro* model was used to evaluate antioxidant activity. This method is based on the principle of increase in the absorbance of the reaction mixture, indicates increase in the antioxidant activity hence increasing reducing power of the samples.

2.6.2. Procedure

The standard drug and test compounds were dissolved in dimethyl for mamide so as to get different concentrations (20 µg/mL to 100 µg/mL). This was mixed with 2.5 mL of (pH 6.6) 0.2 mmol phosphate buffer and 2.5 mL of 1% potassium ferricyanide. The

mixture was incubated at 50°C for 20 min. 2.5 mL of 10% trichloroacetic acid was added to the mixture, which was then centrifuged for 10 min at 1000 rpm. 2.5 mL upper layer of solution was mixed with 2.5 mL of distilled water and 0.5 mL of 0.1% ferric chloride. The absorbance was measured at 700 nm. The absorbance of the blank was also measured in similar manner. The results were compared with ascorbic acid, which was used as a reference standard antioxidant. Results of the antioxidant activities are given in Table 2.

3. RESULTS AND DISCUSSION

The synthesis of the novel compounds 2a-d and 3a-d is described in the above reaction scheme. The reactions were monitored by TLC. The identities of the newly synthesized compounds have been established on the basis of their elemental analysis and spectral data such as IR, ^{1}H NMR and mass spectral studies [33].

Claisen-Schmidt condensation of substituted 2-hydroxy acetophenones (a-d) with benzyloxy benzaldehyde in the presence of 40% NaOH afforded chalcones (1a-d). Reaction of substituted 2-hydroxy chalcones (1a-d) with I_2-DMSO yielded corresponding flavones (2a-d). The IR spectra of 2a showed C-O-C stretching bands at 1123, and 1140 cm^{-1}. The singlet signal obtained on the basis of ^{1}H NMR in 1a at δ 12.65 ppm for −OH proton disappeared in 2a, which confirms that the chalcones have been cyclized; (Figure 1) $FeCl_3$ test for 2a-d was negative which proves the disappearance of phenolic –OH group and formation of a six membered ring containing oxygen atom.

Simultaneously, refluxing chalcones (1a-d) with hydrazine hydrate afforded pyrazolines (3a-d). The formation of 3a was confirmed by the formation of pyrazoline ring. Its IR showed absorption bands at 3307 and 3451 cm^{-1} for –NH and –OH group, respectively. The ^{1}H NMR spectra of 3a showed a characteristic peak of ABX pattern, in the range of δ 2.95-3.02 ppm due to proton H_A, 3.51-3.57 ppm due to H_B proton and third doublet 4.79-4.84 ppm due to H_X proton confirms the formation of pyrazoline ring in 3a. Molecular ion peak $[M]^+$ at 423 confirms the formation of 3a having the molecular formula $C_{22}H_{19}O_2N_2Br$ (Figure 2). Similarly, functional groups of other compounds were confirmed from its IR and physical data mentioned in the experimental section.

3.1. Antibacterial Activity

Some of the synthesized flavones and pyrazoline 2d, 3a, 3b, and 3c were screened for antibacterial activity.

Table 1: Antibacterial activity of synthesized compound.

Compounds	Gram-positive								Gram-negative							
	S. aureus				*B. thuringiensis*				*E. coli*				*E. aerogenes*			
	500	250	125	31	500	250	125	31	500	250	125	31	500	250	125	31
2d	14	12	13	-	21	15	-	-	12	11	7	8	5	-	-	-
3a	12	10	-	-	22	-	18	12	11	-	-	12	-	18	12	-
3b	9	-	7	12	11	19	-	11	12	-	13	7	15	-	5	12
3c	-	20	15	-	10	8	-	-	16	-	9	11	-	-	11	8
Chloramphenicol	30	27	21	20	20	21	16	16	20	18	17	11	16	17	16	15

B. thuringiensis=Bacillus thuringiensis, *E. aerogenes=Enterobacter aerogenes*, *S. aureus=Staphylococcus aureus*

Table 2: Antioxidant activity of flavones and pyrazolines.

Compound code	Absorbance					% increase in absorbance				
	20 µg/ml	40 µg/ml	60 µg/ml	80 µg/ml	100 µg/ml	20 µg/ml	40 µg/ml	60 µg/ml	80 µg/ml	100 µg/ml
Control	0.205					-				
Ascorbic acid	0.231	0.276	0.280	0.304	0.308	12.68	34.63	36.58	48.29	50.24
2a	0.212	0.360	0.209	0.365	0.303	3.41	75.60	1.95	78.05	47.80
2b	0.210	0.218	0.201	0.250	0.390	2.43	6.34	−1.95	21.95	90.24
2c	0.221	0.212	0.268	0.282	0.334	7.80	3.41	30.73	37.56	62.92
2d	0.206	0.215	0.235	0.310	0.316	0.487	4.87	14.6	51.22	54.15
3a	0.210	0.208	0.222	0.277	0.280	2.43	1.46	8.29	35.12	36.58
3b	0.201	0.203	0.238	0.294	0.354	−1.95	−0.976	16.09	43.41	72.68
3c	0.211	0.242	0.266	0.280	0.245	2.92	1.80	29.75	36.58	1.95
3d	0.290	0.265	0.278	0.270	0.326	41.46	29.27	35.61	31.71	59.02

Table 1 shows the inhibition zone calculated at different concentrations from 31 to 500 µg/mL using as the standard drug, chloramphenicol. Data obtained revealed that the test compound 2d, 3a, and 3b are highly active against the *B. thuringiensis*, 3a and 3b against *E. aerogenes*. 3a, 3b, and 3c are moderately active against *E. coli* while 3b and 3c against *S. aureus* at some concentrations. Whereas, rest of the compounds possess poor or found to be inactive against all the test organisms.

3.2. Antioxidant Activity

Flavones 2a-d and pyrazolines 3a-d were assessed for their *in-vitro* antioxidant activities using ascorbic acid as a standard. Significant antioxidant activity was possessed by 2a and 2d. The results reveal that 2b, 2c, 3b, and 3d showed moderate while 3a and 3c gives mild antioxidant activity when compared with ascorbic acid.

4. CONCLUSION

In conclusion, we have synthesized in a simple, readily available, and convenient procedure substituted flavones 2a-d by oxidative cyclization and pyrazolines 3a-d by condensation cyclization, starting from substituted 2-hydroxy chalcones 1a-d. Antibacterial screening of the synthesized compound was done and found to possess excellent activity against some of the selected strains of bacteria while some were found to be moderate and inactive as well. Antioxidant activity of all the synthesized pyrazolines also showed remarkable activity.

5. ACKNOWLEDGMENTS

The Authors are Thankful to the Director, Institute of Science, Nagpur, Principal, Government Science College, Gadchiroli, Research Scholars Mr. Roshan Nasare, Mr. Rahul Taywade, and Mr. Satish Kola for their support and cooperation. The authors are also thankful to the Director, SAIF, Panjab University, Chandigarh for providing CHN analysis, IR, ^{1}H NMR and Mass Spectra.

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