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Original article

Synthesis and antimicrobial studies on novel chloro-fluorine containing hydroxy pyrazolines

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Abstract

A series of chloro-fluorine containing chalcones (**3**) were prepared by Claisen–Schmidt condensation. Chalcone dibromides (**4**) were obtained by the bromination of chalcones at room temperature. Treatment of chalcone dibromides (**4**) with aryloxy acid hydrazides (**5**) in the presence of triethylamine gave chloro-fluorine containing hydroxy pyrazolines (**7**) rather than the expected 1-aryloxy-3-aryl-5-aryl pyrazoles (**6**). The structures of the newly synthesized compounds were confirmed by IR, NMR, mass and elemental analysis. All the compounds were tested for their antibacterial and antifungal activities. Some compounds showed very good antibacterial activity and antifungal activity.

Keywords: 2,4-Dichloro-5-fluorophenyl chalcones; Hydroxy pyrazolines; Antibacterial activity; Antifungal activity

1. Introduction

Chalcones are natural biocides [1] and are well known intermediates for synthesizing various heterocycles. Introduction of halogen into the benzenoid part of α,β-unsaturated ketones enhances the biological activity appreciably [2]. Presence of enone functionality in chalcone confers the antibiotic activity [3,4]. Chalcone dibromides are useful synthons in the synthesis of a large number of bioactive molecules such as pyrazolines, hydroxy pyrazolines, isoxazoles etc.

Pyrazolines are important nitrogen-containing five-membered heterocyclic compounds. Several pyrazoline derivatives possess important pharmacological activities and therefore they are useful materials in drug research. Moreover pyrazolines have played a crucial role in the development of theory in heterocyclic chemistry and also are extensively useful synthons in organic chemistry. Pyrazolines are used as antitumour [5], immunosuppressive [6], antibacterial [7] and antitubercular agents. Some of the pyrazoline derivatives are reported to possess antiinflammatory [8], anticancer [9], antidiabetic [10] and antidepressant properties [11]. Pyrazoline derivatives find applications as dyestuffs, analytical reagents and agrochemicals [12].

Numerous chlorinated organic compounds have various bioactivities which render them as valuable active ingredients of medicines or plant protecting agents. In recent years it is reported that the incorporation of fluorine atom could alter the course of the reaction as well as the biological properties. Introduction of fluoro or CF_3 substituents into a molecule provides compounds with enhanced biological activity. Accumulation of fluorine on carbon leads to increased oxidative and thermal stability. Thus fluorinated drugs are useful due to their being metabolically non-degradable. Further it leads to increased lipid solubility, thereby enhancing the rate of absorption and transport of drug in vivo [13]. Fluorinated pyrazolines and pyrazoles find application as antifertility, antibacterial and antifungal agents [14].

Prompted by the above-mentioned biological properties of pyrazolines, chlorine and fluorine incorporated heterocycles

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it was contemplated to synthesize a novel series of chloro-fluorine containing pyrazoles. However, these reactions produced hydroxy pyrazolines in good yields. Antibacterial and antifungal activity results of the newly synthesized hydroxy pyrazolines are discussed in this paper.

2. Chemistry

1,3-Diaryl-2-propen-1-ones (**3**) were obtained by Claisen–Schmidt condensation of 2,4-dichloro-5-fluoro acetophenone (**1**) with substituted benzaldehydes (**2**). With a view to synthesize 1-aryloxy-3-aryl-5-aryl pyrazoles (**6**), chalcone (**3**) was refluxed with aryloxy acid hydrazide (**5**) in absolute ethanol for several hours, only the starting materials were recovered. In order to facilitate the reaction, chalcones (**3**) were converted to chalcone dibromides (**4**) and were treated with aryloxy acid hydrazides (**5**), there was no forward reaction. When chalcone dibromides (**4**) were treated with aryloxy acid hydrazides (**5**) in the presence of triethylamine in absolute ethanol 1-aryloxy-3-aryl-5-hydroxy-5-aryl pyrazolines (**7**) were obtained rather than the 1-aryloxy-3-aryl-5-aryl pyrazoles (**6**). The reaction sequences and mechanism are outlined in Schemes 1–3.

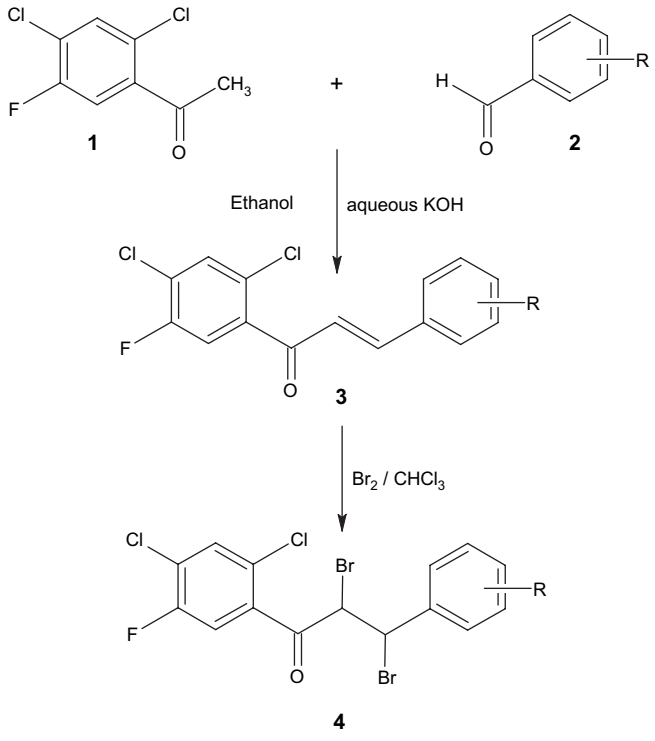
3. Results and discussion

Formation of hydroxy pyrazolines (**7**) was confirmed on the basis of elemental analysis, IR, NMR and mass spectral data.

In the IR spectrum of hydroxy pyrazoline (**7a**), a broad absorption band around 3313 cm^{-1} indicates the presence of hydrogen bonded hydroxyl group in the compound. The amide carbonyl stretching frequency was observed at 1666 cm^{-1}. The shift in the frequency to lower values could be explained on the basis of the mesomeric shift and intramolecular hydrogen bonding. The other prominent absorption bands observed in the IR spectrum are 3095 (Ar–H), 2904 (C–H), 1593 (C=N) and 1463 (C=C) cm^{-1}.

^{1}H NMR spectrum of **7a** showed a singlet at δ 3.59 due to the CH_2 protons attached to *p*-chlorophenoxy moiety. The proton of hydroxyl group resonated as a singlet at δ 4.68. The methylene protons of hydroxy pyrazoline ring appeared as two doublets centered at δ 5.08 and δ 5.15 with a geminal coupling constant ($J = 16.5$ Hz). The appearance of two doublets clearly reveals the magnetic nonequivalence of the two protons of CH_2 group adjacent to a chiral center. The four protons of *p*-chlorophenoxy moiety resonated as two doublets at δ 6.86 ($J = 8.9$ Hz) and 7.22 ($J = 8.9$ Hz). A doublet at δ 7.43 ($J_{H-F\ meta} = 6.7$ Hz) integrating for one proton was attributable to the C_3 proton of 2,4-dichloro-5-fluorophenyl moiety. The protons of phenyl ring resonated as two complex multiplets at δ 7.49–7.50 and 7.74–7.78. The C_6 proton of 2,4-dichloro-5-fluorophenyl moiety resonated as doublet at δ 7.69 ($J_{H-F\ ortho} = 10.2$ Hz).

Further evidence for the formation of hydroxy pyrazolines (**7a**) was obtained by recording the mass spectra. The mass spectrum of compound **7a** showed a molecular ion peak at *m/z* 492 which is in conformity with the molecular formula $C_{23}H_{16}Cl_3FN_2O_3$. The other fragmentation peaks observed at *m/z* are 327 (15%), 191(10%) and 107 (22%). The characterization data of hydroxy pyrazolines (**7a–o**) are given in Table 1.



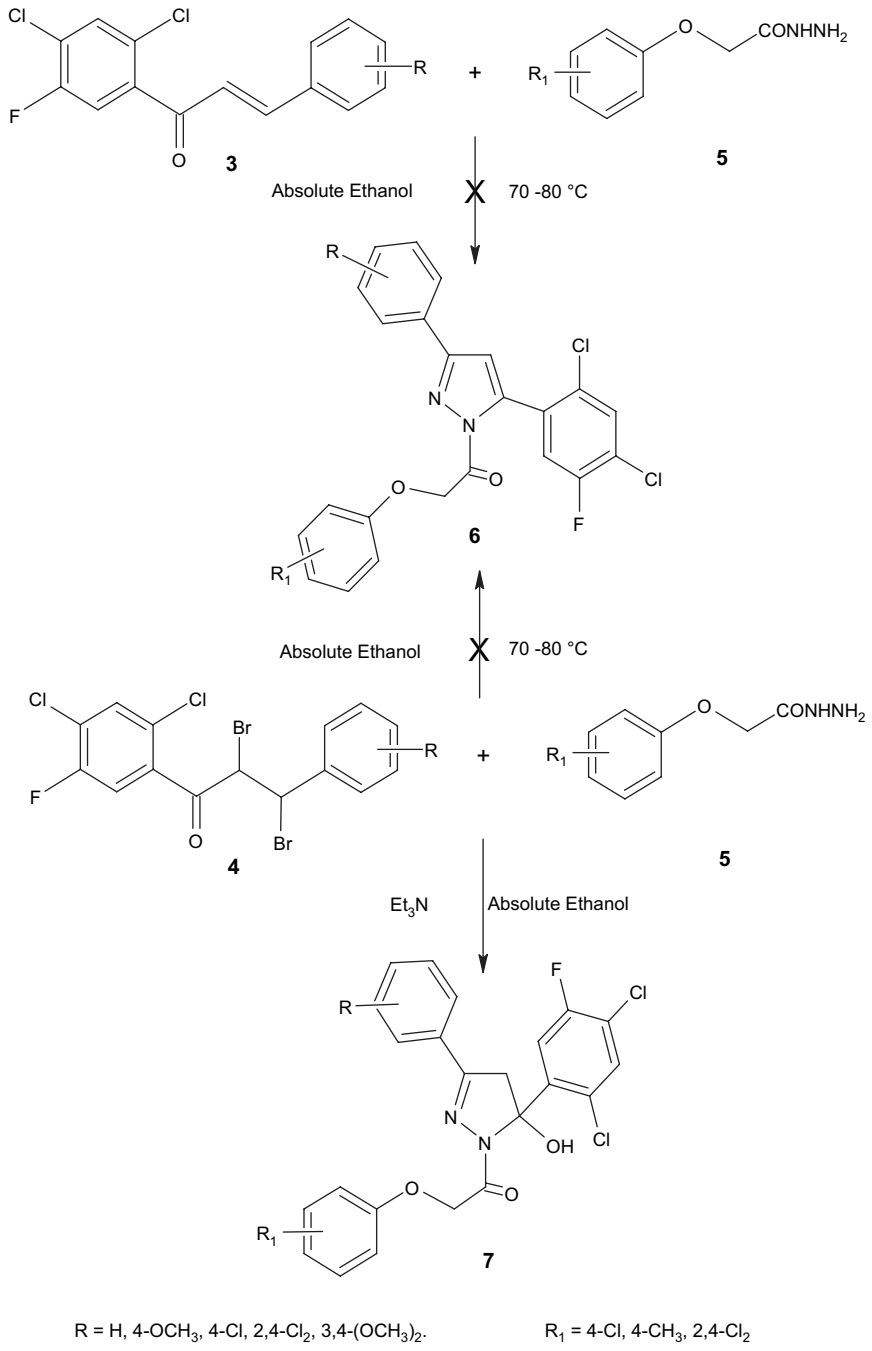
Scheme1. Synthesis of chalcones (**3**) and chalcone dibromides (**4**).

4. Biological activity

4.1. Antibacterial studies

The newly synthesized compounds were screened for their antibacterial activity against *Escherichia coli* (ATCC-25922), *Staphylococcus aureus* (ATCC-25923), *Pseudomonas aeruginosa* (ATCC-27853), *Streptococcus pyogenes* and *Klebsiella pneumoniae* (recultured) bacterial strains by disc diffusion method [15,16]. Discs measuring 6.25 mm in diameter were punched from Whatman no.1 filter paper. Batches of 100 discs were dispensed to each screw capped bottles and sterilized by dry heat at 140 °C for an hour. The test compounds were prepared with different concentrations using dimethylformamide. One milliliter containing 100 times the amount of chemical in each disc was added to each bottle, which contains 100 discs. The discs of each concentration were placed in triplicate in nutrient agar medium seeded with fresh bacteria separately. The incubation was carried out at 37 °C for 24 h. Ciprofloxacin was used as a standard drug. Solvent and growth controls were prepared and kept. Zones of inhibition and minimum inhibitory concentrations (MICs) were noted. The results of antibacterial studies are given in Table 2.

The investigation of antibacterial screening data revealed that all the tested compounds showed moderate to good bacterial inhibition. Compounds **7b**, **7c**, **7d**, **7f**, **7g**, **7h**, **7k** and **7n**

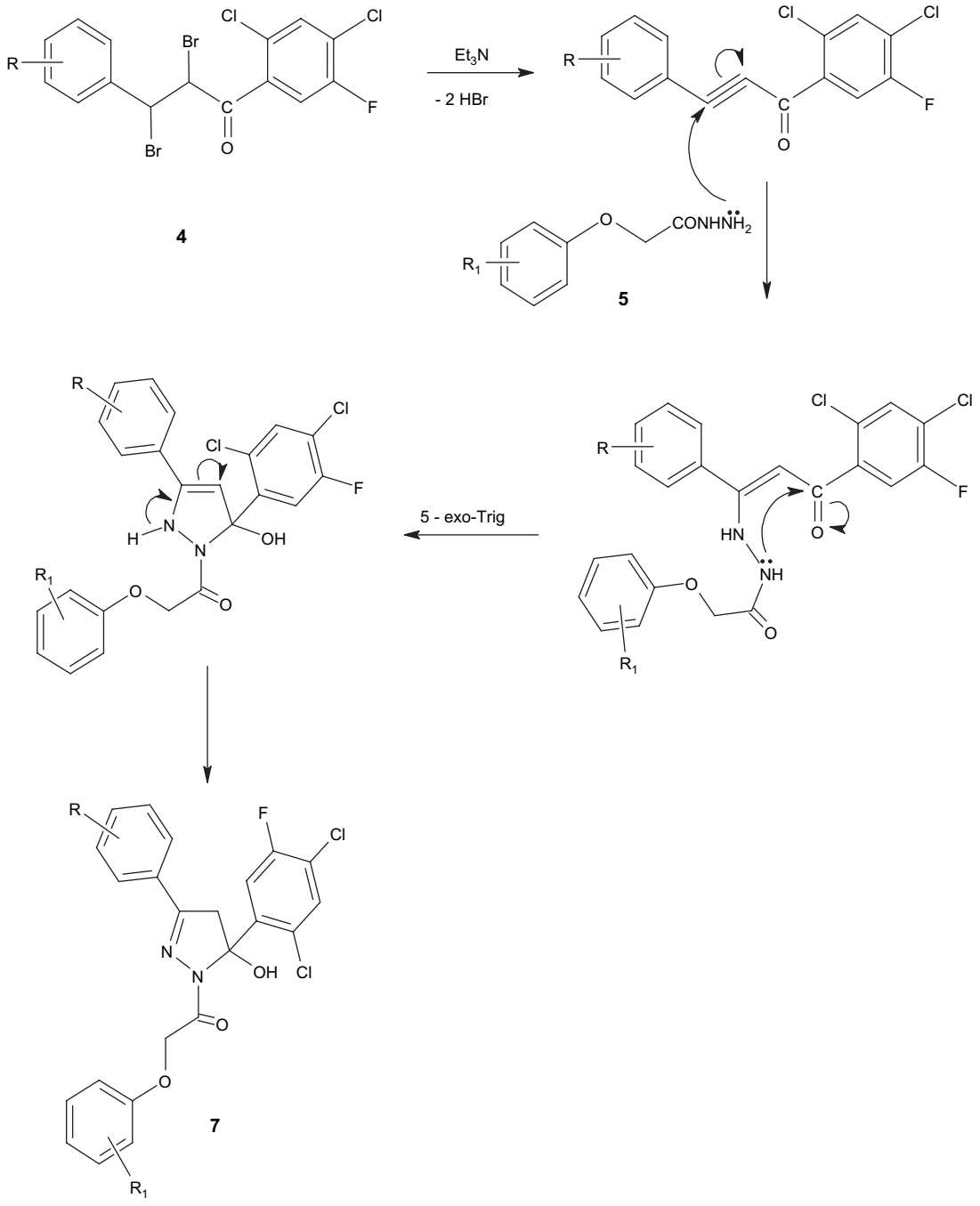


Scheme 2. Expected formation of 1-aryloxy-3-aryl-5-aryl pyrazoles (**6**) and formation of 1-aryloxy-3-aryl-5-hydroxy-5-aryl pyrazolines (**7**).

are active against *E. coli* and *P. aeruginosa* at 12.5 and 6.25 μg/ml concentrations, respectively. Compounds **7b**, **7c**, **7d**, **7f**, **7g**, **7h** and **7k** showed very good activity almost equivalent to that of standard against all the bacterial strains.

4.2. Antifungal studies

Newly prepared compounds were screened for their antifungal activity against *Aspergillus flavus* (NCIM no. 524), *Aspergillus fumigatus* (NCIM no. 902), *Candida albicans* (NCIM no. 300), *Penicillium marneffei* and *Trichophyton mentagrophytes* (recultured) in DMSO by serial plate dilution method [17,18]. Sabourands agar media were prepared by dissolving peptone (1 g), D-glucose (4 g) and agar (2 g) in distilled water (100 ml) and adjusting pH to 5.7. Normal saline was used to make a suspension of spore of fungal strain for lawning. A loopful of particular fungal strain was transferred to 3 ml saline to get a suspension of corresponding species. Agar media (20 ml) were poured into each Petri dish. Excess of suspension was decanted and the plates were dried by placing in an incubator at 37 °C for 1 h. Using an agar punch, wells were made and each wells were labeled. A control was also prepared in triplicate and maintained at 37 °C for 3–4 days. Zone of inhibition and minimum inhibitory concentration (MIC) were



Scheme 3. Mechanism for the formation of 1-aryloxy-3-aryl-5-hydroxy-5-aryl-pyrazolines (**7**).

noted. The activity of each compound was compared with fluconazole as the standard drug. The results of antifungal studies are given in Table 3.

The antifungal screening data showed moderate to good activity but compounds particularly **7d**, **7f**, **7g**, **7h** and **7k** emerged as very active against all the fungal strains.

5. Conclusion

We have synthesized a series of chloro-fluorine bearing 5-hydroxy pyrazolines. The investigation of antibacterial screening data reveals that among the 15 compounds screened seven compounds showed good bacterial inhibition almost equivalent to that of the standard. As far as the antifungal screening results are concerned only five of the compounds displayed good activity. Hydroxy pyrazolines carrying *p*-chlorophenoxy, *p*-cresyloxy and 2,4-dichlorophenoxy moieties at N_1 and combination with phenyl, *p*-anisyl, *p*-chlorophenyl substituents at C_3 position emerged as active in both antibacterial and antifungal screening. Hence, it is concluded that there is ample scope for further study in developing these as good lead compounds.

Table 1
Characterization table of hydroxy pyrazolines (**7a–o**)

Compd no.	R	R′	Mol. formula	m.p (°C)	Yield (%)	Analysis (%)		
						Found (calculated)		
						C	H	N
7a	H	4-Cl	$C_{23}H_{16}Cl_3FN_2O_3$	246–248	87	55.80 (55.92)	3.12 (3.24)	5.56 (5.67)
7b	H	4-CH_3	$C_{24}H_{19}Cl_2FN_2O_3$	230–232	78	60.76 (60.88)	3.88 (4.01)	5.86 (5.91)
7c	H	2,4-Cl_2	$C_{23}H_{15}Cl_4FN_2O_3$	222–224	82	52.20 (52.27)	2.75 (2.84)	5.17 (5.30)
7d	4-OCH_3	4-Cl	$C_{24}H_{18}Cl_3FN_2O_4$	226–228	72	54.87 (55.06)	3.37 (3.44)	5.28 (5.35)
7e	4-OCH_3	4-CH_3	$C_{25}H_{21}Cl_2FN_2O_4$	243–245	76	59.56 (59.64)	4.12 (4.17)	5.45 (5.56)
7f	4-OCH_3	2,4-Cl_2	$C_{24}H_{17}Cl_4FN_2O_4$	231–233	68	51.53 (51.61)	2.96 (3.04)	4.92 (5.01)
7g	4-Cl	4-Cl	$C_{23}H_{15}Cl_4FN_2O_3$	254–256	75	52.13 (52.27)	2.71 (2.84)	5.22 (5.30)
7h	4-Cl	4-CH_3	$C_{24}H_{18}Cl_3FN_2O_3$	259–261	81	56.66 (56.74)	3.45 (3.54)	5.42 (5.51)
7i	4-Cl	2,4-Cl_2	$C_{23}H_{14}Cl_5FN_2O_3$	235–237	77	48.93 (49.06)	2.40 (2.48)	4.93 (4.97)
7j	2,4-Cl_2	4-Cl	$C_{23}H_{14}Cl_5FN_2O_3$	192–194	83	48.91 (49.06)	2.41 (2.48)	4.90 (4.97)
7k	2,4-Cl_2	4-CH_3	$C_{25}H_{17}Cl_4FN_2O_3$	156–158	74	53.05 (53.13)	3.09 (3.13)	5.12 (5.16)
7l	2,4-Cl_2	2,4-Cl_2	$C_{23}H_{13}Cl_6FN_2O_3$	246–248	65	46.12 (46.23)	2.13 (2.17)	4.56 (4.69)
7m	3,4-$(OCH_3)_2$	4-Cl	$C_{25}H_{20}Cl_3FN_2O_5$	134–136	85	54.12 (54.20)	3.55 (3.61)	4.92 (5.05)
7n	3,4-$(OCH_3)_2$	4-CH_3	$C_{26}H_{23}Cl_2FN_2O_5$	226–228	80	58.44 (58.53)	4.25 (4.31)	5.19 (5.25)
7o	3,4-$(OCH_3)_2$	2,4-Cl_2	$C_{25}H_{19}Cl_4FN_2O_5$	244–246	75	50.90 (51.02)	3.16 (3.23)	4.65 (4.76)

6. Experimental protocols

Melting points were determined by open capillary method and are uncorrected. The IR spectra (in KBr pellets) were recorded on a Shimadzu FT-IR 157 spectrophotometer. ^{1}H NMR spectra were recorded either on a Bruker or 300 MHz or 400 MHz NMR spectrometer using TMS as an internal standard. The mass spectra were recorded on an MASPEC low resolution mass spectrometer operating at 70 eV. The purity of the compounds was checked by thin layer chromatography (TLC) on silica gel plate using petroleum ether and ethyl acetate.

*6.1. Procedure for the preparation of 3-aryl-1-(2,4-dichloro-5-fluorophenyl)-2-propen-1-ones (**3**)*

To a mixture of 2,4-dichloro-5-fluoro acetophenone (**1**) (0.01 mol) and substituted benzaldehydes (**2**) (0.01 mol) in ethanol (50 ml), a solution of potassium hydroxide (5%, 25 ml) was added slowly. The mixture was stirred for 24 h. The precipitated solid was filtered, washed with water, dried and recrystallised from ethanol.

*6.2. Procedure for the preparation of 3-aryl-2,3-dibromo-1-(2,4-dichloro-5-fluorophenyl)-2-propen-1-ones (**4**)[19]*

To a solution of 3-aryl-1-(2,4-dichloro-5-fluorophenyl)-2-propen-1-ones (**3**) (0.01 mol) in chloroform (50 ml), bromine (0.01 mol) in chloroform (25 ml) was added slowly with stirring. After the completion of addition of bromine solution, the reaction mixture was stirred for 24 h. Excess of chloroform was distilled off under reduced pressure. The precipitated solid was filtered, dried and recrystallised from chloroform.

Table 2
Antibacterial activities of hydroxy pyrazolines (**7a–o**)

Compd no.	*Staphylococcus aureus*	*Escherichia coli*	*Pseudomonas aeruginosa*	*Klebsiella pneumoniae*	*Streptococcus pyogenes*
7a	14 (12.5)	–	–	10 (25)	–
7b	17 (6.25)	15 (12.5)	18 (6.25)	18 (6.25)	17 (12.5)
7c	15 (6.25)	17 (12.5)	19 (6.25)	16 (6.25)	15 (12.5)
7d	19 (6.25)	18 (12.5)	22 (6.25)	19 (6.25)	18 (12.5)
7e	–	–	10 (25)	–	–
7f	16 (6.25)	16 (12.5)	21(6.25)	16 (12.5)	19 (12.5)
7g	18 (6.25)	18 (12.5)	21 (6.25)	19 (6.25)	20 (12.5)
7h	19 (6.25)	17 (12.5)	24 (6.25)	18 (6.25)	18 (12.5)
7i	–	10 (25)	23 (6.25)	18 (6.25)	–
7j	–	–	–	–	–
7k	19 (6.25)	15 (12.5)	24 (6.25)	18 (6.25)	18 (12.5)
7l	–	17 (12.5)	10 (25)	–	–
7m	–	8 (25)	–	–	10 (25)
7n	–	16 (12.5)	23 (6.25)	–	–
7o	–	9 (25)	–	–	–
Standard	19 (6.25)	18 (12.5)	25 (6.25)	20 (6.25)	20 (12.5)

"–" Indicates bacteria are resistant to the compounds at concentration > 100 μg/ml; MIC values are given in brackets; MIC (μg/ml) = minimum inhibitory concentration, i.e., lowest concentration to completely inhibit bacterial growth; zone of inhibition is expressed in mm.

Table 3
Antifungal activities of hydroxy pyrazolines (**7a–o**)

Compd no.	*Aspergillus fumigatus*	*Aspergillus flavus*	*Trichophyton mentagrophytes*	*Penicillium marneffei*	*Candida albicans*
7a	14 (12.5)	9 (25)	7 (25)	10 (25)	–
7b	11 (12.5)	11 (25)	10 (25)	12 (12.5)	15 (12.5)
7c	13 (12.5)	15 (12.5)	11 (25)	15 (6.25)	10 (25)
7d	21 (6.25)	18 (12.5)	19 (6.25)	20 (6.25)	19 (6.25)
7e	12 (12.5)	–	10 (25)	12 (12.5)	–
7f	19 (6.25)	16 (12.5)	18 (6.25)	20 (6.25)	17 (12.5)
7g	18 (6.25)	16 (12.5)	19 (6.25)	18 (6.25)	20 (12.5)
7h	19 (6.25)	15 (12.5)	20 (6.25)	17 (6.25)	19 (12.5)
7i	–	10 (25)	12 (12.5)	–	–
7j	–	–		10 (25)	–
7k	20 (6.25)	16 (12.5)	18 (6.25)	18 (6.25)	19 (6.25)
7l	–	12 (25)	10 (25)	–	–
7m	–	9 (25)	–	–	10 (25)
7n	–	10 (25)	23 (6.25)	–	–
7o	14 (12.5)	–	–	12 (25)	–
Standard	22 (6.25)	18 (12.5)	20 (6.25)	21 (6.25)	20 (6.25)

"–" Indicates bacteria are resistant to the compounds at concentration > 100 μg/ml; MIC values are given in brackets; MIC (μg/ml) = minimum inhibitory concentration, i.e., lowest concentration to completely inhibit fungal growth; zone of inhibition is expressed in mm.

*6.3. General procedure for the preparation of aryloxy acid hydrazide (**5**)*

Aryloxy acid was prepared from respective phenols. The resulting acid was esterified by treating with absolute ethanol in the presence of few drops of conc. H_2SO_4. Further treatment with hydrazine hydrate yielded aryloxy acid hydrazide (**5**) in good yields.

*6.4. Procedure for the synthesis of 1-aryloxy-3-aryl-5-hydroxy-5-aryl pyrazolines (**7**)*

To a mixture of chalcone dibromides (**4**) (0.01 mol) in absolute ethanol (75 ml) aryloxy acid hydrazides (**5**) (0.01 mol) and triethylamine (10 ml) were added. The reaction mixture was heated under reflux for ~12 h on a water bath. The contents were reduced, cooled and poured onto crushed ice and kept overnight. The resulting hydroxy pyrazolines (**7**) were collected by filtration and recrystallised from suitable solvents.

Compound **7b**: IR (KBr) ν/cm^{-1}: 3303 (OH), 3039 (Ar–H), 2916 (CH_2), 1668 (amide C=O), 1593 (C=N), 1465 (C=C). ^{1}H NMR ($CDCl_3$) δ: 2.27 (s, 3H, CH_3), 3.58 (s, 2H, OCH_2), 4.77 (s, 1H, OH), 5.07 (d, 1H, CH_2, $J = 16.5$ Hz), 5.15 (d, 1H, CH_2, $J = 16.5$ Hz), 6.83 (d, 2H, *p*-cresyloxy protons, $J = 8.2$ Hz), 7.06 (d, 2H, *p*-cresyloxy protons, $J = 8.2$ Hz), 7.42 (d, 1H, dichlorofluorophenyl proton, $J_{H-F\ meta} = 6.6$ Hz), 7.44–7.49 (m, 3H, phenyl protons), 7.69 (d, 1H, dichlorofluorophenyl proton, $J_{H-F\ ortho} = 9.9$ Hz), 7.75–7.78 (m, 2H, phenyl protons).

Compound **7c**: IR (KBr) ν/cm^{-1}: 3398 (OH), 3099 (Ar–H), 1670 (amide C=O), 1571 (C=N), 1471 (C=C). ^{1}H NMR ($CDCl_3$) δ: 3.58 (s, 2H, OCH_2), 4.82 (s, 1H, OH), 5.17 (d, 1H, CH_2, $J = 16.5$ Hz), 5.23 (d, 1H, CH_2, $J = 16.5$ Hz), 6.80 (d, 1H, dichlorophenoxy protons, $J = 8.8$ Hz), 7.13 (dd, 1H, dichlorophenoxy protons, $J = 2.4$ Hz), 7.36 (d, 1H, dichlorophenoxy protons, $J = 2.5$ Hz), 7.43 (d, 1H, dichlorofluorophenyl proton, $J_{H-F\ meta} = 6.6$ Hz), 7.45–7.51 (m, 3H, phenyl protons), 7.71 (d, 1H, dichlorofluorophenyl proton, $J_{H-F\ ortho} = 9.9$ Hz), 7.74–7.77 (m, 2H, phenyl protons). Mass (*m*/*z*, %): 526 (M^+, 25), 493 (76), 460 (28), 191 (12).

Compound **7d**: IR (KBr) ν/cm^{-1}: 3313 (OH), 3099 (Ar–H), 2925 (C–H), 1604 (C=N), 1465 (C=C). ^{1}H NMR ($CDCl_3$) δ: 3.56 (s, 2H, OCH_2), 3.87 (s, 3H, OCH_3), 4.72 (s, 1H, OH), 5.06 (d, 1H, CH_2, $J = 16.4$ Hz), 5.13 (d, 1H, CH_2, $J = 16.4$ Hz), 6.86 (d, 2H, *p*-chlorophenoxy protons, $J = 9$ Hz), 6.97 (d, 2H, *p*-anisyl protons, $J = 8.8$ Hz), 7.21 (d, 2H, *p*-chlorophenoxy protons, $J = 9$ Hz), 7.43 (d, 1H, dichlorofluorophenyl proton, $J_{H-F\ meta} = 6.5$ Hz), 7.67–7.71 (m, 3H, dichlorofluorophenyl proton and *p*-anisyl protons).

Compound **7e**: IR (KBr) ν/cm^{-1}: 3317 (OH), 3091 (Ar–H), 2922 (C–H), 1666 (amide C=O), 1606 (C=N), 1465 (C=C). ^{1}H NMR ($CDCl_3$) δ: 3.55 (s, 2H, OCH_2), 3.87 (s, 3H, OCH_3), 4.83 (s, 1H, OH), 5.04 (d, 1H, CH_2, $J = 16.5$ Hz), 5.13 (d, 1H, CH_2, $J = 16.5$ Hz), 6.83 (d, 2H, *p*-cresyloxy protons, $J = 8.4$ Hz), 6.97 (d, 2H, *p*-anisyl protons, $J = 8.7$ Hz), 7.06 (d, 2H, *p*-cresyloxy protons, $J = 8.4$ Hz), 7.41 (d, 1H, dichlorofluorophenyl proton, $J_{H-F\ meta} = 6.5$ Hz), 7.68–7.72 (m, 3H, dichlorofluorophenyl proton and *p*-anisyl protons). ^{13}C NMR ($CDCl_3$) δ: 20.4, 47.9, 55.4, 65.4, 90.9, 114.3, 116.1, 116.3, 122.9, 125.8, 126.8, 128.4, 128.8, 129.9, 130.6, 131.0, 132.4, 139.7, 154.2, 155.5, 155.9, 158.0, 161.8, 167.5.

Compound **7f**: IR (KBr) ν/cm^{-1}: 3315 (OH), 3099 (Ar–H), 2937 (C–H), 1676 (amide C=O), 1595 (C=N), 1469 (C=C). ^{1}H NMR ($CDCl_3$) δ: 3.55 (s, 2H, OCH_2), 3.87 (s, 3H, OCH_3), 4.68 (s, 1H, OH), 5.15 (d, 1H, CH_2, $J = 16.5$ Hz), 5.21 (d, 1H, CH_2, $J = 16.5$ Hz), 6.79 (d, 1H, dichlorophenoxy protons, $J = 8.8$ Hz), 7.13 (dd, 1H, dichlorophenoxy protons, $J = 2.4$ Hz), 7.36 (d, 1H, dichlorophenoxy protons, $J = 2.5$ Hz), 7.44 (m, 3H, dichlorofluorophenyl proton and *p*-anisyl protons), 7.68 (d, 2H, dichlorofluorophenyl proton and *p*-anisyl protons). Mass (*m*/*z*, %): 556 (M^+, 15), 461 (25), 353 (5), 191 (5).

Compound **7g**: IR (KBr) ν/cm^{-1}: 3303 (OH), 3097 (Ar–H), 2916 (C–H), 1668 (amide C=O), 1593 (C=N), 1463 (C=C). ^1H NMR ($CDCl_3$) δ: 3.55 (s, 3H, OCH_2), 4.73 (s, 1H, OH), 5.06 (d, 1H, CH_2, $J = 16.4$ Hz), 5.10 (d, 1H, CH_2, $J = 16.4$ Hz), 6.86 (d, 2H, *p*-chlorophenoxy protons, $J = 8.9$ Hz), 7.22 (d, 2H, *p*-chlorophenoxy protons, $J = 8.9$ Hz), 7.41–7.45 (m, 3H, dichlorofluorophenyl proton and *p*-chlorophenyl protons), 7.67–7.71 (m, 3H, dichlorofluorophenyl proton and *p*-chlorophenyl protons).

Compound **7h**: IR (KBr) ν/cm^{-1}: 3301 (OH), 3099 (Ar–H), 1668 (amide C=O), 1595 (C=N), 1463 (C=C). ^1H NMR ($CDCl_3$) δ: 2.27 (s, 3H, CH_3), 3.55 (s, 3H, OCH_2), 4.76 (s, 1H, OH), 5.05 (d, 1H, CH_2, $J = 16.5$ Hz), 5.13 (d, 1H, CH_2, $J = 16.5$ Hz), 6.86 (d, 2H, *p*-cresyloxy protons, $J = 8.5$ Hz), 7.06 (d, 2H, *p*-chlorophenyl protons, $J = 8.2$ Hz), 7.41–7.46 (d, 3H, dichlorofluorophenyl proton and *p*-cresyloxy protons), 7.66–7.70 (m, 3H, dichlorofluorophenyl proton and *p*-chlorophenyl protons). Mass (*m*/*z*, %): 506 (M^+, 72), 343 (21), 191 (15).

Compound **7i**: IR (KBr) ν/cm^{-1}: 3323 (OH), 3083 (Ar–H), 1676 (amide C=O), 1593 (C=N), 1469 (C=C). ^1H NMR ($CDCl_3$) δ: 3.55 (s, 2H, OCH_2), 4.74 (s, 1H, OH), 5.15 (d, 1H, CH_2, $J = 16.5$ Hz), 5.20 (d, 1H, CH_2, $J = 16.5$ Hz), 6.79 (d, 1H, dichlorophenoxy protons, $J = 8.8$ Hz), 7.13 (dd, 1H, dichlorophenoxy protons, $J = 2.4$ Hz), 7.36 (d, 1H, dichlorophenoxy protons, $J = 2.4$ Hz), 7.43–7.46 (m, 3H, dichlorofluorophenyl proton and *p*-chlorophenyl protons) 7.68–7.71 (m, 3H, dichlorofluorophenyl proton and *p*-chlorophenyl protons). ^{13}C NMR ($CDCl_3$) δ: 47.8, 66.3, 91.2, 114.2, 116.3, 123.9, 125.6, 126.7, 127.4, 128.0, 128.6, 129.2, 130.3, 132.5, 137.3, 139.1, 152.5, 153.8, 155.7, 158.2, 166.4.

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