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Synthesis, Characterization and Antimicrobial Screening of Some Novel 3-(Naphtalen-1 and 2-yl) -5- Aryl-2-Pyrazolines Synthesized by Condensation of Hydrate Hydrazine to Appropriate α, β-Unsaturated Ketones

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Abstract - Some new pyrazoline derivatives were synthesized by reacting appropriate α, β-unsaturated ketones with hydrate hydrazine in the presence of alcohol. The synthesized compounds were identified by spectral data and screened for antimicrobial activity. Some of these compounds showed moderate to considerable antimicrobial activity.

Keywords: Acetonaphtones, Benzaldehyde, Chalcones, Hydrazine, Pyrazolines, Antimicrobial activity.

INTRODUCTION

Compounds with pyrazoline structures have been reported to possess antimicrobial[1-3], anti-inflammatory [4], antidepressant[5,6], anti-tumoral[7] activities. Among various pyrazoline derivatives, 2-pyrazolines seem to be the most frequently studied. A variety of methods have been reported for the preparation of this class of compounds. In the present study, some new pyrazoline derivatives **(9-16)**

have been synthesized by reacting appropriate α,β-unsaturated ketones with hydrazine hydrate in the presence of alcohol. The structures of the various synthesized compounds are assigned on the basis of elemental analysis, IR and ^{1}H ,^{13}C NMR spectral data. These compounds were also screened for their antibacterial and antifungal activities.

Experimental:

General Remarks: Melting points were determined on a capillary melting point apparatus and are uncorrected. Analytical thin layer chromatography (TLC) was conducted on percolated TLC plates (silica gel 60F254, Merck) visualized under UV light and stained with either phosphomolybdic acid or *p*-anisaldehyde. ^{1}H and ^{13}C NMR spectra are recorded on a Brüker spectrometer respectively at 400 and at 100 MHz in $CDCl_3$ and DMSO (internal standard TMS, δ = 0.0 ppm) at room temperature. The following abbreviations were used to explain the multiplicities: s = singlet, dd = doublet doublet, m = multiplet. Infrared spectra were recorded in KBr on Perkin-Elmer AC-1 spectrophotometer. Microanalyses were performed on Carlo Erba EA- 1108 element analyzer and were within the ±0.4% of the theoretical values. Column chromatography was performed on silica gel (Merck, 60-120 mesh).

General procedure for the preparation of 2-pyrazolines (9-16): (*P-and o,p*-substituted benzyliden)-acrylonaphtones **(1-8)** (0.001 mol) were dissolved in 20 mL of ethanol. Hydrazine hydrate (8 mL) was added to the mixture drop wise. After that, the mixture was refluxed for 12 hours. The reaction mixture was poured into ice-cold water and the solid mass that separated out was filtered, dried and recrystallized from ethanol.

3-(naphtalen-1-yl) -5- (4-isopropylphenyl)-2-pyrazoline (9): A white crystal (70% Yield).^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.23 (d, *J* = 6.9 Hz, 6H), 2.90 (sept, *J* = 6.9 Hz ,1H), 3.32 (dd, *J* = 4.6, 17.7 Hz, 1H), 3.82 (dd, *J* = 11.8, 17.7 Hz, 1H), 5.52 (dd, *J* = 4.6, 17.7 Hz, 1H), 7.32-7.42 (m, 5H Ar), 7.53-7.81 (m, 4H Ar), 7.85-7.88 (m, 2H Ar). ^{13}C NMR (100 MHz, $CDCl_3$):δ : 23.90, 23.92, 33.77, 42.60, 58.80, 125.62, 126.69, 127.08, 128.81, 130.62, 130.97, 137.94, 148.59, 155.55. Anal. calcd. for $C_{22}H_{26}N_2$: C, 82.45; H, 8.81; N, 8.74. Found: C, 82.40; H, 8.77; N, 8.70%.

3-(naphtalen-1-yl) -5- (4-chlorophenyl)-2-pyrazoline (10): A white crystal (80% Yield).^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.23 (dd, *J* = 18.4, 4.8 Hz, 1H), 3.70 (dd, *J* = 18.4, 11.9 Hz, 1H), 4.96 (dd, *J* = 11.9, 4.8, 1.0 Hz, 1H), 7.33-7.44 (m, 5H Ar), 7.55-7.83 (m, 4H Ar), 7.84-7.87 (m, 2H Ar). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 41.75, 59.03, 125.71, 126.75, 127.25, 128.91, 131.42, 131.72, 139.14, 148.09, 155.25. Anal. calcd. for $C_{19}H_{19}ClN_2$: C, 72.95; H, 6.77; N, 8.95. Found: C, 72.91; H, 6.73; N, 8.91%.

3-(naphtalen-1-yl) -5- (4-methylphenyl)-2-pyrazoline (11): A white crystal (87% Yield).^{1}H NMR (400 MHz, $CDCl_3$) δ:1.20 (s, 3H), 3.27 (dd, *J* = 18.3, 4.8 Hz, 1H), 3.82 (dd, *J* = 18.3, 11.8 Hz, 1H), 5.53 (dd, *J* = 11.8, 4.8, 1.0 Hz, 1H), 7.30-7.45 (m, 5H Ar), 7.48-7.52 (m, H Ar), 7.68-7.72 (m, 2H Ar). ^{13}C NMR (100 MHz, $CDCl_3$) δ:23.86,42.40, 57.70, 125.60, 126.59, 127.02, 128.80, 130.59, 130.95, 137.86, 148.48, 155.83. Anal. calcd. for $C_{20}H_{22}N_2$: C, 82.15; H, 8.27; N, 9.58. Found: C, 82.11; H, 8.23; N, 9.54%.

3-(naphtalen-1-yl) -5- (2,4-dihydroxyphenyl)-2-pyrazoline (12) : A white crystal (76% Yield).^{1}H NMR (400 MHz, DMSO) δ : 3.29 (dd, *J* = 18.4, 4.8 Hz, 1H), 3.81 (dd, *J* = 18.4, 11.9 Hz, 1H), 5.51 (dd, *J* = 11.9, 4.8, 1.0 Hz, 1H), 7.27-7.47 (m, 5H Ar), 7.48-7.53 (m, 3H Ar), 7.58-7.62 (m, 2H Ar), 10.08 (2H, s, OH). ^{13}C NMR (100 MHz, DMSO) δ: 42.54, 58.79, 125.61, 126.65, 127.05, 128.81, 130.62, 130.97, 138.94, 147.69, 154.75. Anal. calcd. for $C_{19}H_{22}N_2O_2$: C, 73.52; H, 7.14; N, 9.03. Found: C, 73.48; H, 7.10; N, 9.00%.

3-(naphtalen-2-yl) -5- (4-isopropylphenyl)-2-pyrazoline (13): A white crystal (70% Yield).^{1}H NMR (400 MHz, $CDCl_3$) δ : 1.23 (d, *J* = 6.9 Hz, 6H), 2.90 (sept, *J* = 6.9 Hz ,1H), 3.32 (dd, *J* = 4.6,

17.7 Hz, 1H), 3.82 (dd, *J* = 11.8, 17.7 Hz, 1H), 5.52 (dd, *J* = 4.6, 17.7 Hz, 1H), 7.32-7.42 (m, 5H Ar), 7.54-7.79 (m, 4H Ar), 7.85-7.88 (m, 2H Ar). ^{13}C NMR (100 MHz, $CDCl_3$):δ : 23.90, 23.92, 33.77, 42.60, 58.80, 125.62, 126.69, 127.08, 128.81, 130.62, 130.97, 137.94, 148.59, 155.55. Anal. calcd. for $C_{22}H_{26}N_2$: C, 82.97; H, 8.23; N, 8.80. Found: C, 82.93; H, 8.20; N, 8.76%.

3-(naphtalen-2-yl) -5- (4-chlorophenyl)-2-pyrazoline (14): A white crystal (82% Yield).^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.23 (dd, *J* = 18.4, 4.8 Hz, 1H), 3.70 (dd, *J* = 18.4, 11.9 Hz, 1H), 4.96 (dd, *J* = 11.9, 4.8, 1.0 Hz, 1H), 7.33-7.44 (m, 5H Ar), 7.52-7.82 (m, 4H Ar), 7.84-7.87 (m, 2H Ar). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 41.98, 58.89; 125.71, 126.75, 127.25, 128.91, 131.42, 131.72, 139.14, 148.09, 155.25. Anal. calcd. for $C_{19}H_{19}ClN_2$: C, 73.42; H, 6.16; N, 9.01. Found: C, 73.38; H, 6.12; N, 8.98%.

3-(naphtalen-2-yl) -5- (4-methylphenyl)-2-pyrazoline (15): A white crystal (57% Yield).^{1}H NMR (400 MHz, $CDCl_3$) δ : 1.20 (s, 3H), 3.27 (dd, *J* = 18.3, 4.8 Hz, 1H), 3.82 (dd, *J* = 18.3, 11.8 Hz, 1H), 5.53 (dd, *J* = 11.8, 4.8, 1.0 Hz, 1H), 7.30-7.45 (m, 5H Ar), 7.467.50 (m, 4H Ar), 7.68-7.72 (m, 2H Ar). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 23.85, 42.40, 57.70, 125.60, 126.59, 127.02, 128.80, 130.59, 130.95, 137.86, 148.48, 155.83. Anal. calcd. for $C_{20}H_{22}N_2$: C, 82.72; H, 7.64; N, 9.65, Found: C, 82.68; H, 7.60; N, 9.61%.

3-(naphtalen-2-yl) -5- (2,4-dihydroxyphenyl)-2-pyrazoline (16): A brown crystal (62% Yield).^{1}H NMR (400 MHz, DMSO) δ : 3.29 (dd, *J* = 18.4, 4.8 Hz, 1H), 3.81 (dd, *J* = 18.4, 11.9 Hz, 1H), 5.51 (dd, *J* = 11.9, 4.8, 1.0 Hz, 1H), 7.27-7.47 (m, 5H Ar), 7.48-7.51 (m, 3H Ar), 7.58-7.62 (m, 2H Ar), 10.08 (2H, s, OH). ^{13}C NMR (100 MHz, DMSO) δ: 41.95, 58.79, 125.61, 126.65, 127.05, 128.81, 130.62, 130.97, 138.94, 147.69, 154.75. Anal. calcd. for $C_{19}H_{22}N_2O_2$: C, 74.00; H, 6.54; N, 9.08. Found: C, 73.96; H, 6.50; N, 9.04%.

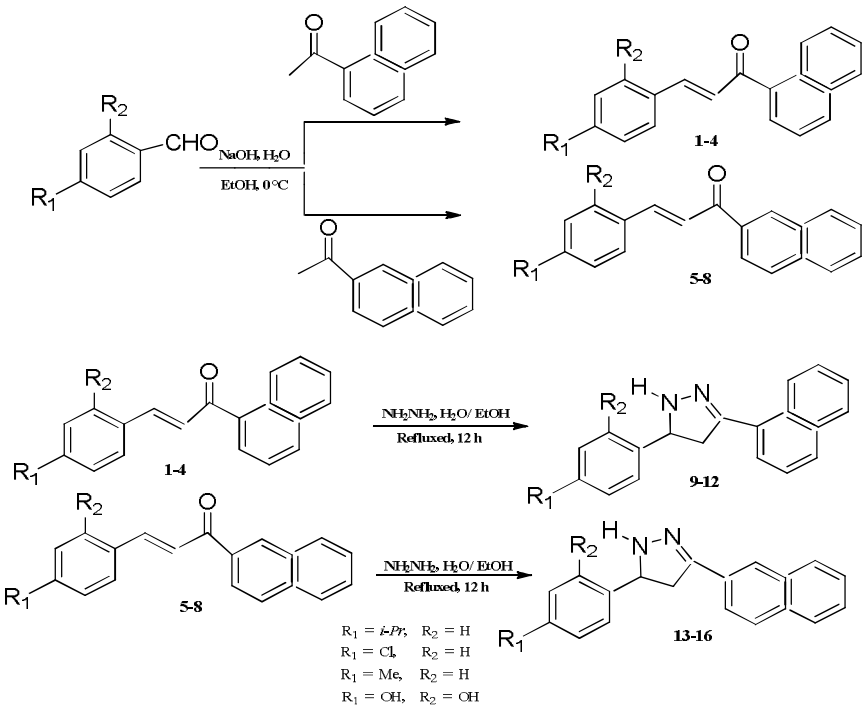
Antimicrobial activity: The synthesized compounds **(9-16)** were screened *in vitro* for antibacterial activity against *Escherichia coli, Salmonella typhi, Staphylococcus aureus and Bacillus subtilis* at the concentrations 200, 300, 400 and 500 µg/mL and for antifungal activity against *Aspergillus Niger* at 100, 200, 300, 400 µg/mL by cup plate agar diffusion method[8]. The concentrations used in screening were chosen after determining the MICs of each compound. The solvent used was dimethylsulfoxide (DMSO) further diluted with water. Müller-Hinton agar was used as the growth medium for the bacterial species and Sabouraud's agar was the growth medium for the fungal species. DMSO was used as a control for all the type of microorganisms. The control showed no activity against the strains of microorganisms used. The results presented in Tables 1 and 2 are obtained after 48 hours of incubation at 35 °C for antibacterial test and at 28-30 °C for antifungal test. They are compared with standard drugs penicillin for antibacterial activity and Greseofulvin for antifungal activity by measuring the zone of inhibition in mm.

In summary, we were able to synthesize in this work a series of 2-pyrazolines derivatives. They showed an activity against the strains of microorganisms used. The two isomers **10** and **14** having chloro group as pharmacophore is present in one moiety exhibited antimicrobial activity proving probably the relation between structure and activity. The data reported in this article may be helpful guide for the medicinal chemist who is working in this area.

RESULTS AND DISCUSSION

Treatment of compounds **(1-8)** with commercial hydrazine hydrate in ethanol under reflux afforded the corresponding 2-pyrazolines derivatives as 3-(naphtalen-1 and-2-yl)-5- aryl-2-pyrazolines **(9-16)**. The progress of these reactions could be easily monitored by TLC showing a complete transformation of starting materials to single products, which were easily isolated by cooling at < 0 °C and filtration

of the precipitated solid. Highly pure products were isolated in this manner and were crystallized from ethanol. They were identified by FT-IR and high field NMR spectroscopy. The FT-IR spectrum of these compounds exhibited bands due to: C=N of pyrazoline ring at 1630 cm^{-1}, C=C at 1601 cm^{-1} and C-N at 1250 cm^{-1}. Furthermore, their ^1H NMR spectra in $CDCl_3$ (DMSO) displayed the characteristic ABX three-spin system of the neighboring methylene and methyne protons of the pyrazoline ring, 4.96-5.52 ppm (dd, H_X), 3.70-3.82 ppm (dd, H_B) and 3.23-3.32 ppm (dd, H_A). The ^{13}C NMR spectra of all the compounds **(9-16)** corroborated the 1*H*-pyrazole structure with the signals of carbon atoms C-3 (154-156 ppm), C-4 (41-43 ppm) and C-5 (57-59 ppm). **Scheme 1.**



Scheme 1. Synthesis of pyrazoline derivatives **(9-16)**

The compounds **(9-16)** were screened for their antibacterial activity against *Escherichia. coli, Salmonella typhi, Staphylococcus aureus* and *Bacillus subtilus* by using paper disc diffusion method[8] using penicillin (100 µb/disc) as reference standard and antifungal activity against *Aspergillus Niger*, *Aspergillus flavus*, *Penicillium chrysogenum* and *Fusirium moneliforme* by using *Greseofluvim* (100 µb/disc). The observed Minimum Inhibitory Concentrations (MIC) values for all the synthesized compounds are presented in **Tables 1 and 2**. The investigation of antibacterial screening results indicates that compounds **10**, **11**, **15**, **16** show promising activity and compounds **9**, **12**, **13**, **14** poor activity against *E. coli*. Compounds **10**, **11**, **15**, **16** show good activity against *Salmonella typhi*. Compounds **10**, **11** and **15** show high activity and compound **9** shows low activity against *Staphylococcus Areus*. The table 2 indicates that compounds **9**, **10**, **11**, **13**, **15** and **16** show inhibitory effect against *A. Niger* and compounds **10**, **11**, **14** and **16** show inhibitory effects against *A. flavus* Compounds **11**, **12**, **14** and **16** show inhibitory effects against *P. chrysogenum*, similar compounds 11

and 15 show inhibitory effect against *F. moneliforme*. Remaining compounds are inactive against all the fingers. Results are show in Tables 1 and 2.

Table 1: Antibacterial screening results of the compounds **(9-16)**

Compound	*Escherichia Coli*	*Salmonella typhi*	*Staphylococcus Areus*	*Bacillus subtilus*
9	08	10	13	11
10	13	17	25	16
11	14	19	27	18
12	10	13	22	12
13	10	10	18	24
14	9	11	14	22
15	14	18	26	17
16	15	20	21	19
Penicillin	18	25	40	17
DMSO	-	-	-	-

-No antibacterial activity

Table 2: Antifungal screening results of the compounds **(9-16)**

Compound	*Aspergillus Niger*	*Aspergillus flavus*	*Pencillium chrysogenum*	*Fusirium moneliforme*
9	-	+	+	+
10	-	-	+	+
11	-	-	-	-
12	+	+	-	+
13	-	+	+	+
14	+	-	-	+
15	-	+	+	-
16	-	-	-	+
Greseofulvin	-	-	-	-
Control	+	+	+	+

- No Growth: Antifungal activity **+ Growth: No Antifungal activity**

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