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Synthesis, characterization and antibacterial activity of some new 2-pyrazolines using triethanolamine as reaction solvent

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ABSTRACT

In present investigation, a series of 2-pyrazolines (**2a-P**) were prepared by cyclization of hydrazine hydrate/ phenyl hydrazine with α, β-unsaturated ketone (chalcones) using triethanolamine solvent within 15-20 min.The newly synthesized 2-pyrazolines were characterized on the basis of elemental analysis and spectroscopic data. All newly synthesized compounds were evaluated for their antibacterial activity. Most of the compounds showed potent activity.

Keywords: Halohydroxychalcones, hydrazine hydrate/phenyl hydrazine, triethanolamine, 2-pyrazolines, antibacterial activity.

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INTRODUCTION

Due to the interesting activity of variously substituted pyrazolines as biological agents considerable attention has been focused on this class. The pharmaceutical importance of these compounds lies in the fact that they can be effectively utilized as antimicrobial, antinociceptive, antiviral, antidepressant, antiamoebic, tranquillizing, immunosuppressive, anti-arthirtic and antimycobacterial agents [1-9]. Some of these compounds have also anti-inflammatory, antidiabetic and anaesthetic properties [10-12]. In addition, pyrazolines have played a crucial part in the development of theory in heterocyclic chemistry and also used extensively in organic synthesis [13-15].In view of these interesting biological activities it was thought worthwhile to develop new class of these compounds.

RESULTS AND DISCUSSION

In continuation of our research interest in synthesis of some bioactive heterocyclic compounds [16], herein, we would like to report a simple, efficient and rapid method for the synthesis of 2-pyrazolines by the condensation of chalcones with hydrazine hydrate/ phenyl hydrazine in triethanolamine within 15-20 min.

Chalcones **1(a-h)** were prepared by conventional Claisen-Schmidt condensation of 2-Chloro-6-methyl-quinoline-3-carbaldehyde and substituted acetophenones [17]. The 2-pyrazolines **2(a-P)** were attempted by reacting chalcones with hydrazine hydrate/ phenyl hydrazine hydrate in presence of triethanolamine within 15-20 min. The structures of newly synthesized compounds were established on the basis of spectroscopic data and elemental analysis.

The result of antibacterial activity data are shown in Table 2. In comparison with standard drug, compounds **2e, 2f, 2k, 2n** and **2o** showed better activity against all the tested bacteria. Compounds **2h** and **2p** showed nearly equal activity Bacillus subtilis and Ervinia carotovara than standard Ampicillin drug. While remaining compounds showed moderate to good antibacterial activity.

MATERIALS AND METHODS

Experimental

Melting points were uncorrected and determined in an open glass capillary tube. IR spectra were recorded on FTIR Shimadzu spectrometer. ^{1}H NMR spectra were recorded in DMSO on Avance 300 MHz spectrometer using TMS as an internal standard. The mass spectra were recorded on VG 7070H spectrometer using ionization energy of 70eV. Elemental analyses were performed on a Carlo Erba 106 Perkin-Elmer model 240 analyzer.

Typical procedure for synthesis of 2-Pyrazolines (2a-p)

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A mixture of 1a (0.01mol) and hydrazinehydrate / phenyl hydrazinehydrate (0.02 mol) were dissolved in triethanolamine (TEA) and refluxed for 15-20 min (Table-1).The progress of reaction was monitored by TLC. After completion of reaction, reaction mixture was poured in ice cold water. The solid separated was filtered, washed and then crystallized from mixture of ethyl alcohol and DMF (60:40).

3-(2'-Hydroxy-3', 5'-diiodophenyl)-5-(2-Chloro-6-methylquinolinyl)-2-pyrazoline (2a)

IR (KBr): 3332 (>N-H), 1590 (C=N); ^{1}HNMR (DMSO-d_6): δ 2.40 (s, 3H, CH_3),δ 3.32 (s,1H, H_A), δ 3.90 (s, 1H, H_B), δ 5.54(s, 1H, H_X), δ 7.05(s, 1H, NH), δ 7.15-8.20 (m, 6H, Ar-H), 12.55 (s, 1H, -OH) ppm; M.S. (m/z): 589.5 (m+), 591.5 (M+2); Anal.Calcd.for $C_{19}H_{14}OCl\ I_2N_3$: C, 38.67; H, 2.37; N, 7.12%. Found: C, 38.55; H, 2.27; N, 7.03%.

3-(5'-Chloro-2'-hydroxy-3'-iodophenyl)-5-(2-Chloro-6-methylquinolinyl)-2-pyrazoline (2c)

IR (KBr): 3329 (>N-H), 1598 (C=N); ^{1}HNMR (DMSO-d_6): δ 2.44 (s, 3H, CH_3),δ 3.34 (s,1H, H_A), δ 3.94 (s, 1H, H_B), δ 5.50(s, 1H, H_X), δ 7.02(s, 1H, NH), δ 7.10-8.10 (m, 6H, Ar-H), 12.65 (s, 1H, -OH) ppm; M.S. (m/z): 498 (m+), 500 (M+2), 502 (M+4); Anal.Calcd.for $C_{19}H_{14}OCl\ I_2N_3$: C, 38.67; H, 2.37; N, 7.12%. Found: C, 38.55; H, 2.27; N, 7.03%.

3-(2'-Hydroxy-3'-iodo-5'-mehtylphenyl)-5-(2-Chloro-6-methylquinolinyl)-2-pyrazoline (2d)

IR (KBr): 3333 (>N-H), 1599 (C=N); ^{1}HNMR (DMSO-d_6): δ 2.40 (s, 3H, CH_3), δ 2.49 (s, 3H, CH_3), δ 3.37 (s,1H, H_A), δ 3.95 (s, 1H, H_B), δ 5.52(s, 1H, H_X), δ 6.99(s, 1H, NH), δ 7.16-8.13 (m, 6H, Ar-H), δ 12.61 (s, 1H, -OH) ppm; M.S. (m/z): 477.5 (m+), 479.5 (M+2); Anal.Calcd.for $C_{20}H_{17}OClIN_3$: C, 50.26; H, 3.56; N, 8.79%. Found: C, 50.38; H, 3.62; N, 8.85%.

3-(2',4'-dihydroxy-3'5'-diiodophenyl)-5-(2-Chloro-6-methylquinolinyl)-2-pyrazoline (2f)

IR (KBr): 3330 (>N-H), 1590 (C=N); ^{1}HNMR (DMSO-d_6): δ 2.40 (s, 3H, CH_3), δ 3.35 (s,1H, H_A), δ 3.93 (s, 1H, H_B), δ 5.54(s, 1H, H_X), δ 7 (s, 1H, NH), δ 7.19-8.12 (m, 5H, Ar-H), δ 8.25(s, 1H, -OH), δ 12.61 (s, 1H, -OH) ppm; M.S. (m/z): 605.5 (m+), 607.5 (M+2); Anal.Calcd.for $C_{19}H_{14}O_2Cl\ I_2N_3$: C, 37.65; H, 2.31; N, 6.39%. Found: C, 37.53; H, 2.40; N, 6.48%.

3-(2',4'-dihydroxy-3'5'-dichlorophenyl)-5-(2-Chloro-6-methylquinolinyl)-2-pyrazoline (2g)

IR (KBr): 3328 (>N-H), 1592 (C=N); ^{1}HNMR (DMSO-d_6): δ 2.37 (s, 3H, CH_3), δ 3.33 (s,1H, H_A), δ 3.95 (s, 1H, H_B), δ 5.55(s, 1H, H_X), δ 7.02 (s, 1H, NH), δ 7.19-8.15 (m, 5H, Ar-H), δ 8.27(s, 1H, -OH), δ 12.67 (s, 1H, -OH) ppm; M.S. (m/z): 422.5 (m+), 424.5 (M+2), 426.5 (M+4), 428.5 (M+6) ; Anal.Calcd.for $C_{19}H_{14}O_2Cl_3N_3$: C, 53.96; H, 3.31; N, 9.94%. Found: C, 54.05; H, 3.38; N, 10.02%.

3-(2'-Hydroxy-3', 5'-diiodophenyl) -5- (2-Chloro-6-methylquinolinyl) -1- phenyl-2-pyrazoline (2i)

IR (KBr):1595 (C=N); ^{1}HNMR (DMSO-d_6): δ 2.43 (s, 3H, CH_3),δ 3.35 (s,1H, H_A), δ 3.93 (s, 1H, H_B), δ 5.51(s, 1H, H_X), δ 7.08-8.25 (m, 11H, Ar-H), δ 12.68 (s, 1H, -OH) ppm; M.S. (m/z): 665.5 (m+), 667.5 (M+2); Anal.Calcd.for $C_{25}H_{18}OCl\ I_2N_3$: C, 45.07; H, 2.70; N, 6.31%. Found: C, 44.99; H, 2.79; N, 6.37%.

3-(4'-Hydroxy-3',5'-diiodophenyl)-5-(2-Chloro-6-methylquinolinyl)-1-phenyl-2-pyrazoline (2j)

IR (KBr):3480 (-OH),1600 (C=N); ^{1}HNMR (DMSO-d_6): δ 2.40 (s, 3H, CH_3),δ 3.33 (s,1H, H_A), δ 3.93 (s, 1H, H_B), δ 5.53(s, 1H, H_X), δ 7.10-8.29 (m, 11H, Ar-H), δ 8.35(s, 1H, -OH) ppm; M.S. (m/z): 665.5 (m+), 667.5 (M+2); Anal.Calcd.for $C_{25}H_{18}OCl\ I_2N_3$: C, 45.07; H, 2.70; N, 6.31%. Found: C, 44.98; H, 2.79; N, 6.39%.

3-(5'-Chloro-2'-hydroxy-3'-iodophenyl)-5-(2-Chloro-6-methylquinolinyl)- 1-phenyl-2-pyrazoline (2k)

IR (KBr): 1595 (C=N); ^{1}HNMR (DMSO-d_6): δ 2.38 (s, 3H, CH_3),δ 3.36 (s,1H, H_A), δ 3.92 (s, 1H, H_B), δ 5.48(s, 1H, H_X), δ 7.15-8.21 (m, 11H, Ar-H), 12.67 (s, 1H, -OH) ppm; M.S. (m/z): 574 (m+), 576 (M+2), 578 (M+4); Anal.Calcd.for $C_{25}H_{18}OCl_2I\ N_3$: C, 52.26; H, 3.13; N, 7.31%. Found: C, 52.35; H, 3.17; N, 7.36%.

3-(2'-Hydroxy-3'-iodo-5'-mehtylphenyl)-5-(2-Chloro-6-methylquinolinyl)-1-phenyl -2-pyrazoline (2l)

IR (KBr): 1596(C=N); ^{1}HNMR (DMSO-d_6): δ 2.39 (s, 3H, CH_3), δ 2.47 (s, 3H, CH_3), δ 3.39 (s,1H, H_A), δ 3.93 (s, 1H, H_B), δ 5.55(s, 1H, H_X), δ 7.19-8.27 (m, 11H, Ar-H), δ 12.71 (s, 1H, -OH) ppm; M.S. (m/z): 553.5 (m+), 555.5 (M+2); Anal.Calcd.for $C_{26}H_{21}OClIN_3$: C, 56.36; H, 3.79; N, 7.58%. Found: C, 56.44; H, 3.85; N, 7.65%.

3-(2',4'-dihydroxy-3'5'-dichlorophenyl)-5-(2-Chloro-6-methylquinolinyl)- 1-phenyl -2-pyrazoline (2o)

IR (KBr): 1600 (C=N); ^{1}HNMR (DMSO-d_6): δ 2.39 (s, 3H, CH_3), δ 3.36 (s,1H, H_A), δ 3.95 (s, 1H, H_B), δ 5.53(s, 1H, H_X), δ 7.20-8.25 (m, 10H, Ar-H), δ 8.35 (s, 1H, -OH), δ 12.72 (s, 1H, -OH) ppm; M.S. (m/z): 498.5 (m+), 500.5 (M+2), 502.5 (M+4), 504.5 (M+6) ; Anal.Calcd.for $C_{25}H_{18}O_2Cl_3N_3$: C, 60.18; H, 3.61; N, 8.42%. Found: C, 60.07; H, 3.67; N, 8.50%.

3-(2',4'-dihydroxy-3'5'-dibromophenyl)-5-(2-Chloro-6-methylquinolinyl)-2-pyrazoline (2p)

IR (KBr): 1595 (C=N); ^{1}HNMR (DMSO-d_6): δ 2.39 (s, 3H, CH_3), δ 3.35 (s,1H, H_A), δ 3.90 (s, 1H, H_B), δ 5.55(s, 1H, H_X), δ 7.20-8.30 (m, 10H, Ar-H), δ 8.37(s, 1H, -OH), δ 12.70 (s, 1H, -OH) ppm; M.S. (m/z): 587.5 (m+), 589.5 (M+2), 591.5 (M+4), 593.5 (M+6); Anal.Calcd.for $C_{25}H_{18}O_3ClBr_2N_3$: C, 51.06; H, 3.06; N, 7.14%. Found: C, 51.13; H, 2.99; N, 7.20%.

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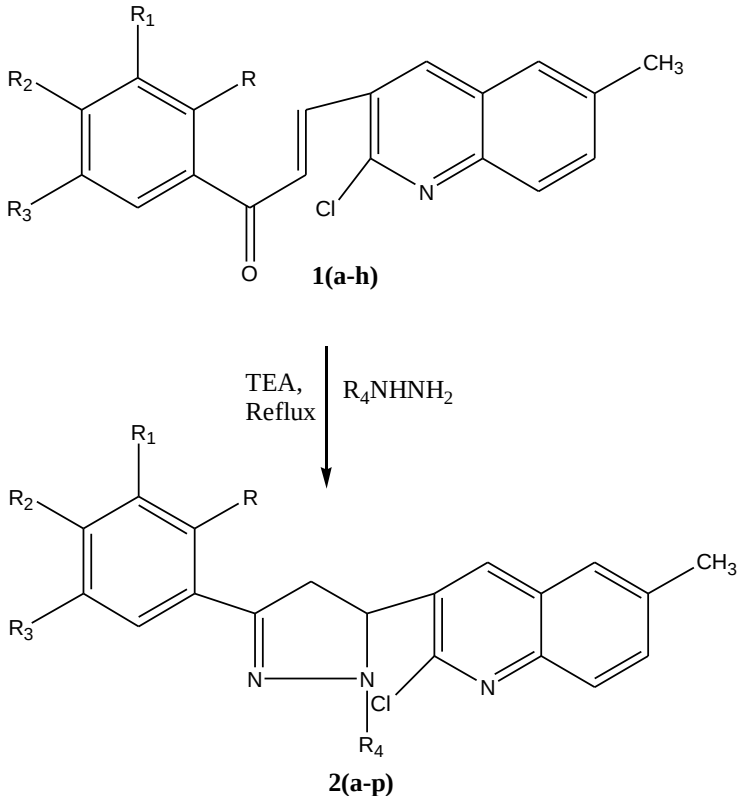
Scheme: Synthesis of Pyrazolines.



CONCLUSIONS

We have synthesized a series of some novel 2-pyrazolines by condensation of substituted chalcones with hydrazine hydrate / phenyl hydazinehydrate in triethanolamine within 15-20 min.The investigations of antibacterial screening data reveals that among the 16 compounds screened seven compounds showed good bacterial inhibition almost equivalent to that of the standard. Hence, it is concluded that there is ample scope for further study in developing these as good lead compounds.

Table 1: Yield and Physical data of synthesized products (2a-p)

Entry	Product	R	R_1	R_2	R_3	R_4	Time (min.)	Yield (%)	M.P. (^{0}C)
1	**2a**	OH	I	H	I	H	15	77	191-193
2	**2b**	H	I	OH	I	H	15	71	178-179
3	**2c**	OH	I	H	Cl	H	17	69	194-196

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4	**2d**	OH	I	H	CH_3	H	15	75	169-171
5	**2e**	OH	Br	H	Cl	H	20	71	171-173
6	**2f**	OH	I	OH	I	H	15	78	178-179
7	**2g**	OH	Cl	H	Cl	H	18	80	195-197
8	**2h**	OH	Br	H	Br	H	18	74	172-174
9	**2i**	OH	I	H	I	C_6H_5	15	72	193-195
10	**2j**	H	I	OH	I	C_6H_5	20	78	199-201
11	**2k**	OH	I	H	Cl	C_6H_5	18	68	147-149
12	**2l**	OH	I	H	CH_3	C_6H_5	15	70	168-170
13	**2m**	OH	Br	H	Cl	C_6H_5	18	74	171-73
14	**2n**	OH	I	OH	I	C_6H_5	20	75	184-186
15	**2o**	OH	Cl	H	Cl	C_6H_5	20	73	190-192
16	**2p**	OH	Br	H	Br	C_6H_5	20	69	152-154

Table 2: Antibacterial activity of synthesized compounds 2(a-p)

Products	**A**	**B**	**C**	**D**

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2a	**17**	**15**	**20**	**17**
2b	**19**	**17**	**21**	**14**
2c	**24**	**22**	**25**	**22**
2d	**20**	**20**	**15**	**18**
2e	**26**	**24**	**27**	**26**
2f	**27**	**23**	**28**	**24**
2g	**28**	**24**	**25**	**27**
2h	**24**	**16**	**23**	**18**
2i	**15**	**18**	**14**	**15**
2j	**17**	**16**	**19**	**17**
2k	**25**	**23**	**25**	**23**
2l	**16**	**19**	**14**	**18**
2m	**21**	**16**	**20**	**14**
2n	**27**	**25**	**27**	**26**
2o	**25**	**26**	**28**	**25**
2p	**23**	**18**	**25**	**17**
Reference	**27**	**26**	**28**	**25**

Zone of inhibitions are expressed in mm. **A =** *Bacillus subtilis* (Bs), **B** = *Escherichia coli* (E.coli), **C** = *Ervinia carotovara* (Ec), **D =** *Xanthomanas citri* (Xc), **Reference =** Ampicillin

Antimicrobial activity

The antimicrobial activities of the synthesized compounds 2(a–p) were determined by agar well diffusion method [18]. The compounds were evaluated for antibacterial activity against *Bacillus subtilis* (Bs), *Escherichia coli* (E.coli), *Ervinia carotovara* (Ec) and *Xanthomanas citri* (Xc). The antibiotic Ampicillin (25 μg/mL) was used as reference drug for antibacterial and antifungal activity. Dimethyl sulphoxide (1%, DMSO) was used a control without compound.

The culture strains of bacteria were maintained on nutrient agar slant at 37 ± 0.5°C for 24 h. The antibacterial activity was evaluated using nutrient agar plate seeded with 0.1 mL of respective bacterial culture strain suspension prepared in sterile saline (0.85%) of 10^5 CFU/ mL dilutions. The wells of 6 mm diameter were filled with 0.1 mL of compound solution at fixed concentration 25 μg/mL separately for each bacterial strain. All the plates were incubated at 37 ± 0.5°C for 24 h. Zone of inhibition of compounds in mm were noted.

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