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Microwave Assisted Synthesis of Novel 2-Pyrazolines From Furan Based Chalcones and Study their Anti-microbial Activity

SANTOSH LAXMAN KUMBHARE[1]* and YUVRAJ KHUSHAL MESHRAM[2]

[1]Department of Chemistry, Shri Shivaji Science & Arts College, Chikhli, Dist. Buldana (M.S.), 443201, India.
[2]Department of Chemistry, G.S. College, Khamgaon, Dist., Buldana (M.S.), 444303, India.
*Corresponding author E-mail: infoslkumbhare@yahoo.com

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ABSTRACT

Nitrogen heterocyclic compounds such as 2-pyrazoline showing various pharmacological activities such as anti-bacterial, anti-fungal, anti-oxidant, anti-depressant, anti-inflammatory, anticancer, and anti-tubercular activities. This promotes to synthesize 2-pyrazolines by the reaction of different substituted chalcones of 2-Acetyl furan and hydrazinehydrate in the presence alcohol. Synthesized compound was confirmed by physical data such as melting point and various spectral analysis such as FTIR, NMR spectra. Anti-microbial activity of synthesized compound was evaluated. The results indicated that some of compounds show good antibacterial and antifungal activity.

Keywords: Pyrazolines, 2-Acetyl Furan, Chalcones, Physical data, Spectral data, Anti-microbial activity, Anti-fungal activity.

INTRODUCTION

The pyrazolines are important heterocyclic compounds containing two adjacent nitrogen atom in five membered heterocyclic ring with one endocyclic double bond on[1,2] position. It has been found that various pyrazoline derivative reported various potential biological activities such asanti-microbial, anti-oxidant, anti-cancer, anti-tumor, antitu-bercular, anti-depressant, activities. Pyrazolines containing different heteroaromatic substituent have showed a broad spectrum of biological activities and thus highly useful for preparation of new pharmacophore agents having improved biological activity. Pyrazoline and heterocyclic moiety such as furan, thiophene, pyridine, quinoline, indole possess important and domineering bioactivities, which condense them useful biomolecules in drug research.

Medicinal chemist have carried out considerable research for synthesis of novel antimicrobial agents carrying pyrazoline and heterocyclic moiety. Bio steric replacement approach was used for designing the compounds. The bio steric replacement of benzene with heteroaromatic ring resulted different microbial agents having

the same biological activity. Heteroaromatic ring such as furan, thiophene, pyridine, quinoline, indole used as ring equivalents to benzene in drug research. Various researchers have synthesized and evaluated the pyrazoline derivativescarrying pyrazoline and heterocyclic moiety.

Many heterocyclic chalcone derivatives were synthesized for biological studies[1-4]. Different 1,3,5-trisubstitutedpyrazoline derivatives were showed sensible anti-bacterial and anti-fungal activity[5]. It was found that different nitrofuryl pyrazoline derivatives were found to possess antibacterial activity[6]. Some of nitrofuryl containing pyrazolines are used in preserving fish sausages but due to toxicity, nitrofuryl pyrazolines derivatives, has been discouraged[7]. To reduce toxicity arylfurans introduce in place of Nitrofuran[8]. It was found furan derivatives are known to be associated with multiple biological activities[9–11]. Keeping these observations for preparation of novel N-bridged heterocyclic compounds[12-15], different substituted furan pyrazoline hybrid compounds carryingfuran and pyrazoline in single molecule were synthesized and studied their antimicrobial activity.

MATERIALS AND METHODS

Chemicals required for preparation are of analytical grade and purchased from Merck Private limited, Mumbai. The melting point were uncorrected and determined by open capillaries, using Thiels tube. TLC paper (Merck grade) were used to monitor the progress of reaction. FTIR spectra obtained from IR Spectrometer by using KBr pelletstechniques. The IR frequencies are expressed in cm^{-1}. The ^{1}HNMR spectra of the compounds were obtained from 500 MHz spectrophotometer using Tetramethyl silane as an internal standard and DMSO as a solvent.

Synthetic method for preparation of chalcone derivarives from 2-Acetyl Furan

A mixture of 2-Acetyl Furan (0.01 mol) and appropriate aldehydes (0.01mol) was dissolved in minimum quantity of alcohol. Heat the reaction mixture at about 60^{0}C and then add 40% NaOH slowly with constant stirring about 45 minutes. Keep the mixture overnight and then pour in to ice cold water and if necessarythen acidify with dil. HCl, the solid chalcone obtained. Filter it and recrystallized by ethyl alcohol. Determine its Melting point. TLC used to check the purity of each synthesized using n-Hexane and Ethyl acetate (6:4) as a solvent system.

Microwave assisted synthesis of 3(furan-2-yl) -5-Phynyl-2-Pyrazoline derivatives (Figure 1)

A mixture of Chalcone (0.01 mol) and Hydrazine hydrate (0.02 mol) in ethanol (20 mL) was irradiated under Microwave oven at 600 watt 2-4 minutes. Cool the mixture and pour in crushed ice, the solid obtained. Determine its Melting point.TLC used to check the purity of each synthesized using n-Hexane and Ethyl acetate (6:4) as a solvent system.

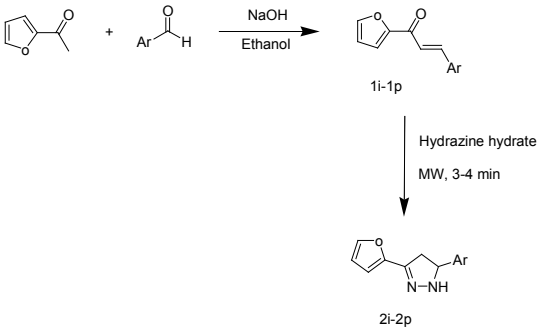

Fig. 1. Scheme for synthesis of 3(furan-2-yl)-5-Phynyl-2-Pyrazolines

Detection method

All synthesized pyrazolines (2i-2p) were detected by their Physical data and Spectral analysis as shown below.

3(Furan-2-yl)-5-(4-Chloro phenyl)-2-Pyrazoline (2i)

Molecular Formula $C_{13}H_{11}N_2OCl$, Molecular weight 246.5, %Yield=85, m.p.=135^{0}C FT-IR (KBr disc): 3331(Pyrazoline N-H); 3080(Aromatic C–H), 1640(C=N), 1250(C–N), 1620(C=C), 750 (C–Cl), ^{1}HNMR: 3.29(dd, 1H, CH_2 (Pyraz)), 5.17(dd, 1H, CHPyraz), 6.44(d,1H, CH_{furyl}), 7.45-8.00(dd, 4H, Ar-H), 10, 2(s, 1H, N-H).

3(Furan-2-yl)-5-(4-Bromo phenyl)-2-Pyrazoline (2k)

Molecular Formula $C_{13}H_{11}N_2OBr$, Molecular weight 291g, %Yield=90, m.p.=170^{0}C FT-IR (KBr disc): 3320(Pyrazoline N-H), 1593(ring C=N), 1564(ring C=C), 1483(ring N-N), 1126(C-N), 1063 (C-O-C), 803(C-Br), ^{1}H-NMR: 3.28(dd,1H, CH_2 (Pyraz)), 5.16(dd, 1H, CHPyraz), 6.43(d,1H, CH_{furyl}), 7.40-8.00(dd, 4H, Ar-H), 10.3(s, 1H, N-H).

3(Furan-2-yl)-5-(4-Fluoro phenyl)-2-Pyrazoline (2l)

Molecular Formula $C_{13}H_{11}N_2OF$, Molecular

weight 229, %Yield=80, m.p.=200^{0}C FT-IR (KBr disc): 3307(Pyrazoline N-H),) 1590(ring C=N), 1563(ring C=C), 1480(ring N-N), 1122(C-N), 1065(C-O-C), 1110(C-F), ^{1}H-NMR: 3.23(dd, 1H, CH_2 (Pyraz)), 5.15 (dd, 1H, CHPyraz), 6.37(d,1H, CH_{furyl}), 7.45-8.00(dd, 4H, Ar-H), 10, 2(s, 1H, N-H).

3(Furan-2-yl)-5-(4-methoxy phenyl)-2-Pyrazoline (2m)

Molecular Formula $C_{14}H_{14}O_2N_2$, Molecular weight 242, %Yield=140, m.p.=140^{0}C FT-IR (KBr disc): 3315(Pyrazoline N-H), 1595(ring C=N), 1566(ring C=C), 1487(ring N-N), 1125(C-N), 1067 (C-O-C), 1158(C-O), ^{1}H-NMR: 3.46(dd, 1H, CH_2 (Pyraz)), 3.67(s,3H, OCH_3) 5.17(dd, 1H, CHPyraz), 6.24(d, 1H, CH_{furyl}), 7.50-8.00(dd, 4H, Ar-H), 10, 2 (s, 1H, N-H).

3(Furan-2-yl)-5-(4-ethoxy phenyl)-2-Pyrazoline (2n)

Molecular Formula $C_{15}H_{16}O_2N_2$, Molecular weight 256, %Yield=78, m.p.=160^{0}C FT-IR (KBr disc): 3315(Pyrazoline N-H), 1595(ring C=N), 1566(ring C=C), 1487(ring N-N), 1125(C-N), 1067(C-O-C), 1158(C-O) ^{1}H-NMR: 3.25(dd, 1H, CH_2 (Pyraz)), 3.65 (s,3H, OCH_3) 5.17(dd, 1H, CH Pyraz), 6.40(d, 1H, CH_{furyl}) 7.56-8.00(dd, 4H, Ar-H), 10, 2(s, 1H, N-H).

3(Furan-2-yl)-5-(4-Nitro phenyl)-2-Pyrazoline (2o)

Molecular Formula $C_{13}H_{11}N_3O_3$, Molecular weight 257, %Yield=90, m.p.=240^{0}C, FT-IR (KBr disc): 3315(Pyrazoline N-H), 1595(ring C=N), 1566(ring C=C), 1487(ring N-N), 1125 (C-N), 1067(C-O-C), 1158(C-O), ^{1}H-NMR 2.74(dd, 1H,CH), 3.30(dd, 1H, CH), 3.75(s, 3H, OCH_3), 4.80(t, 1H, CH Ar), 6.85 (d, 1H, CH_{furyl}), 7.05(m, 7H, Ar), 10.5(s, 1H, N-H).

3(Furan-2-yl)-5-(4-methyl phenyl)-2-Pyrazoline (2p)

Molecular Formula $C_{14}H_{14}N_2O$, Molecular weight 226, %Yield=79, m.p.=210^{0}C FT-IR (KBr disc): 3312(Pyrazoline N-H), 1594(ring C=N), 1543(ring C=C), 1480(ring N-N), 1122(C-N), 1065(C-O-C), 1150(C-O), ^{1}H-NMR: 3.40(dd, 1H, CH_2(Pyraz), 3.80(s, 3H, OCH_3) 5.18(dd, 1H, CH Pyraz), 6.53(d, 1H, CH_{furyl}), 7.83(dd, 4H, Ar-H), 10.3(s, 1H, N-H).

RESULTS

As per standard procedure the agar medium and peptone water was prepared. Test solution was prepared in DMSO. Cup Plate Method using Muller-Hinton agar medium was employed to study the preliminary anti-bacterial activity of compound (2i-2p) against *Staphylococcus aureus*, *Streptococcus faecalis*, *E. coli*, *P. fluorescenes* screened by Cup plate method using Muller-Hinton agar medium. OFLOXACIN (10 mg) was employed as a reference standard drug to compare antibacterial activity of synthesized comounds. The pH of all the test solutions and control was kept at 2-3 by using Conc. HCl.

Antifungal activity of compound (2i-2p) against Trichophyton rubrum and *Candida albicans* screened by Cup plate method using PDA (Potato-Dextrose-Agar) medium. As per standard procedure nutrient broth, subculture, base layer medium and PDA medium was prepared. Test solution was prepared in DMSO. OFLOXACIN (10 mg) was employed as a reference standard drug to compare antifungal activity of synthesized comounds. The pH of all the test solutions and control was kept 2-3 by using Conc. HCl.

In the petri dishes, the test solution of compound, control and reference standards were added separately and subsequently incubated at 37^{0}C for 24 h for antibacterial activity and kept aside at room temperature for 48 h for antifungal activity. Zone of inhibition produced by each compound was measured in mm and the results are presented in Table 1 for antibacterial activity and Table 2 for

Table 1: Anti-bacterial Activity of 2-Pyrazoline (2i-2p)

Sr. No	Compound	Zone of inhibition in mm			
		S. aureus	*S. faecalis*	*E. coli*	*P. fluorescenes*
1	2i	20	16	23	18
2	2k	Resistance	Resistance	Resistance	Resistance
3	2l	14	Resistance	18	Resistance
4	2m	20	13	Resistance	14
5	2n	18	12	Resistance	13
6	2o	Resistance	Resistance	Resistance	Resistance
7	2p	Resistance	Resistance	Resistance	Resistance
8	Control DMSO	--	--	--	--
9	Reference OFIOXACIN	20	10	10	12

Table 2: Antifungal Activity of 2-Pyrazoline (2i-2p)

Sr. No	Compound	Zone of inhibition in mm	
		Trichophyton rubrum	*Candida albicans*
1	2i	20	14
2	2k	Resistance	12
3	2l	Resistance	12
4	2m	Resistance	13
5	2n	Resistance	12
6	2o	Resistance	Resistance
7	2p	Resistance	Resistance
8	Control DMSO	10 mm	8
9	Reference OFIOXACIN	14 mm	--

antifungal activity.

DISCUSSION

The compound (2i-2p) synthesized were screened for their antibacterial (Table 1) and antifungal activity (Table 2). Table 1 showed 2i was found to be resistance against highly sensitive against *Staphylococcus aureus*, highly sensitive against *Streptococcus faecalis*, resistance against *E. coli* and highly sensitive against *Pseudomonas fluorescens*. Compound 2k was found to be highly sensitive against *Staphylococcus aureus*, *Streptococcus faecalis, Pseudomonas fluorescens* and resistance against *E. coli*. Compound 2l was found to be resistance against *Staphylococcus aureus*, *Streptococcus faecalis* and highly sensitive against *E. coli* and *Pseudomonas fluorescens*. Compound 2m was found to be highly sensitive against *Staphylococcus aureus, E. coli* and resistance against *Streptococcus faecalis*, *Pseudomonas fluorescens*. Compound 2n was found to be resistance against *Staphylococcus aureus*, *E. coli* and highly sensitive against *Streptococcus faecalis, Pseudomonas fluorescens*. Compound 2o was found to be resistance against *Staphylococcus aureus, Streptococcus faecalisand* highly sensitive against *E.coli*, *Pseudomonas fluorescens*. Compound 2p was found to be highly sensitive against *Staphylococcus aureus* and moderately sensitive against *Pseudomonas fluorescens*, resistance against *Streptococcus faecalis*, *E. coli*.

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