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SYNTHESIS OF PYRAZOLINES (substituted 4,5-dihydro-5-(2-methoxynaphthalen-6-yl)-1*H*-pyrazol-3-yl)(phenyl) USING ALUM [KAl $(SO_4)_2.12H_2O$] AS AN EFFICIENT AND NOVEL CATALYST AND THEIR MICROBIOLOGICAL ACTIVITY

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ABSTRACT

Herein we report, Synthesis of Pyrazolines using alum as a novel catalyst. Alum [KAl $(SO4)_2 \cdot 12H_2O$] performs as a novel catalyst for the synthesis of Pyrazolines from various substituted Chalcones [various substituted (E)-3-(2-methoxynaphthalen -6-yl)-1-phenylprop-2-en-1-one)] in good to excellent isolated yield (60–76%) using ethanol as a solvent for reaction. The remarkable advantages offered by this method is an inexpensive and easily available catalyst, a simple procedure, mild reaction conditions and faster the reactions. The structures of synthesized compounds elucidated using IR Spectroscopy, Mass Spectrometry, ^{1}H NMR Spectroscopy and ^{13}C Spectroscopy.

Keywords: Pyrazolines, Alum, Substituted Chalcones, Microbiological activity

INTRODUCTION

Pyrazolines are used as anti-microbial, anti-inflammatory, analgesic, insecticidal, herbicidal agent's, synthetically useful scaffolds in organic synthesis. In asymmetric synthesis, chiral Pyrazolines behaves as precursors.

The reaction of chalcones and related α, β-unsaturated ketones with phenyl hydrazine is probably the most popular and efficient procedure for the synthesis of 2-pyrazolines. The reaction can be conducted under various conditions **[1]**. The reaction of chalcones and related α, β-unsaturated ketones with phenyl hydrazine is efficient procedure for the synthesis of 2-pyrazolines **[2]**. The second breakthrough came in early twentieth century when reaction of the diazoalkanes with unsaturated carboxylic acid derivatives **[3-6]** and enones **[7-8]** was realized. Among diazoalkanes, diazomethane proved to be the most convenient nitrogen containing reagent making available the preparation of a wide variety of 1-pyrazolines as primary products, which spontaneously isomerizes or can be converted into appropriate 2-pyrazoline isomers **[9-13]**. The reaction of chalcones and related α, β-unsaturated ketones with phenyl hydrazine is probably the most popular and efficient procedure for the synthesis of 2-pyrazolines. The reaction can be conducted under various conditions **[14-16]**. Pyrazoline derivatives have also been synthesized by a new protocol from vinyl compounds having electron withdrawing group at terminal position. The transformation is brought about by ethyl diazoacetate as a reagent in presence of DABCO or $InCl_3$ as a catalyst **[17]**.

Alum has been used at least since Roman times for purification of drinking water and industrial process water **[18]**, recently various substituted Chalcones have been synthesized using Alum **[19]**.

Experimental Section:

Chalcones [substituted (*E*)-1-(2-hydroxyphenyl)-3-(2-methoxy naphthalen-6-yl)prop-2-en-1-one] (0.00030 mol) is dissolved in 10 volume of ethanol containing alum (100 mol%). To this reaction mixture, (0.00039 mol) of hydrazine hydrate is added. The reaction mass is heated for 4 hr between 80°C and 85°C. After completion of reaction (checked by TLC), reaction mixture is cooled below 30°C. Cold water is slowly added to the flask and the separated solid product was filtered and washed with cold water for several times. The final compound is crystallized using ethanol. Material is dried in oven at temperature below 35°C.

Using above methodology series of compounds [substituted (4,5-dihydro-5-(2-ethoxy

naphthalen-6-yl)-1*H*-pyrazol-3-yl)(phenyl) methanone] have been synthesized **(M1B to M9B)**, procedure for the preparation of one compound is provided below **(Figure 1)**.

Procedure for synthesis of 2-(5-(6-Methoxynaphthalen-2-yl)-4,5-dihydro-1*H*-pyrazol-3-yl)phenol (M1B):

Obtained *(E)*-1-(2-hydroxyphenyl)-3-(2-methoxynaphthalen-6-yl) prop-2-en-1-one (0.1gm, 0.00030 mol) is dissolved in 2 ml of ethanol containing alum (100 mol). To this reaction mixture, (0.019 ml, 0.00039 mol) of hydrazine hydrate is added. The reaction mass is heated for 4 hr between 80°C and 85°C. After completion of reaction (checked by TLC), reaction mixture is cooled below 30°C. 10 mL cold water is slowly added to the flask and the separated solid product is filtered and washed with cold water for several times. Obtained final compound 2-(5-(6-Methoxynaphthalen-2-yl)-4,5-dihydro-1*H*-pyrazol-3-yl) phenol is crystallized using ethanol. Material is dried in oven at temperature below 35°C.

Structure of the compounds M1B-M9B confirmed by the different spectroscopic techniques [IR Spectroscopy, Mass Spectrometry, ^{1}H NMR Spectroscopy and ^{13}C Spectroscopy], interpretation of representative compound (M1B) is provided below:

- **Melting Point (°C):** Between 120°C and 122°C
- **Mass (m/z)**: 317$[M+H]^{+}$
- **^{1}H NMR δppm (DMSO-d6)**: 7.78-7.69 (m,3H), 7.60 (d,1H),7.47 (d,1H), 7.26-7.12 (m, 2H), 6.86 (d,2H), 5.96 (b, 1H), 5.53 (b,1H), 5.04 (t,1H), 3.53-3.07 (m, 1H), 3.92 (s,3H)
- **^{13}C NMR δppm ($CDCl_3$)**: 157.88, 151.41, 137.85, 134.25, 132.99, 129.41, 128.87,128.64, 127.77, 126.14, 124.94, 119.25, 105.82, 64.47, 55.39, 41.45
- **IR (KBr)cm^{-1}**: 3380 (O-H stretch), 2957 (N-H stretching), 1594 (C=C aromatic), 1160 (C-OH stretch)

Synthetic scheme:

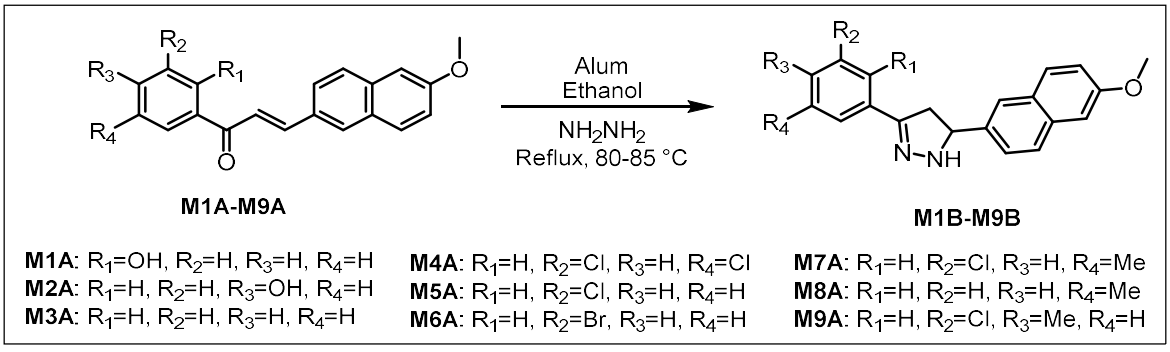
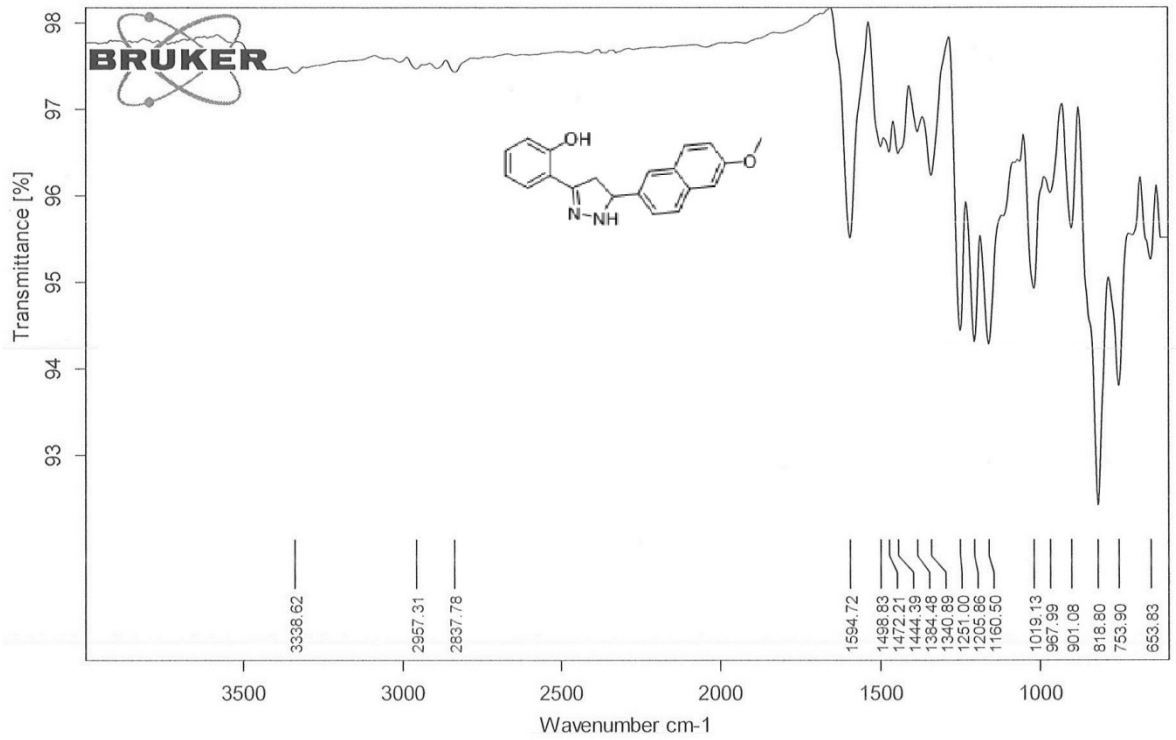
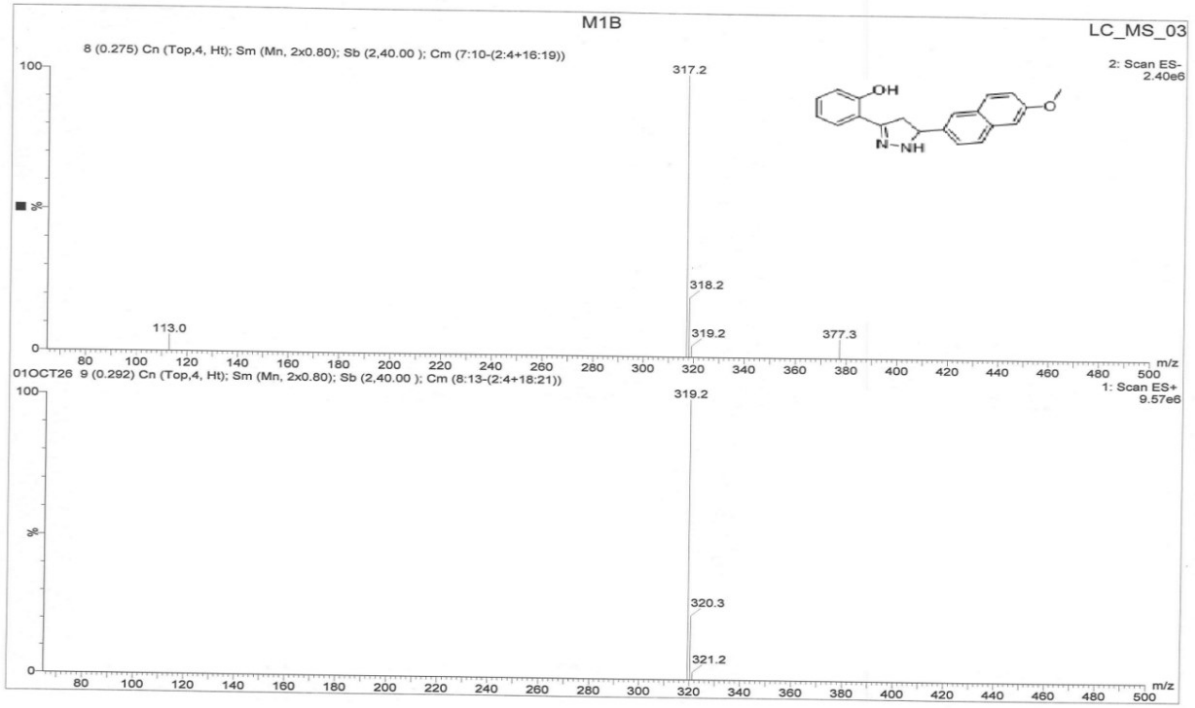


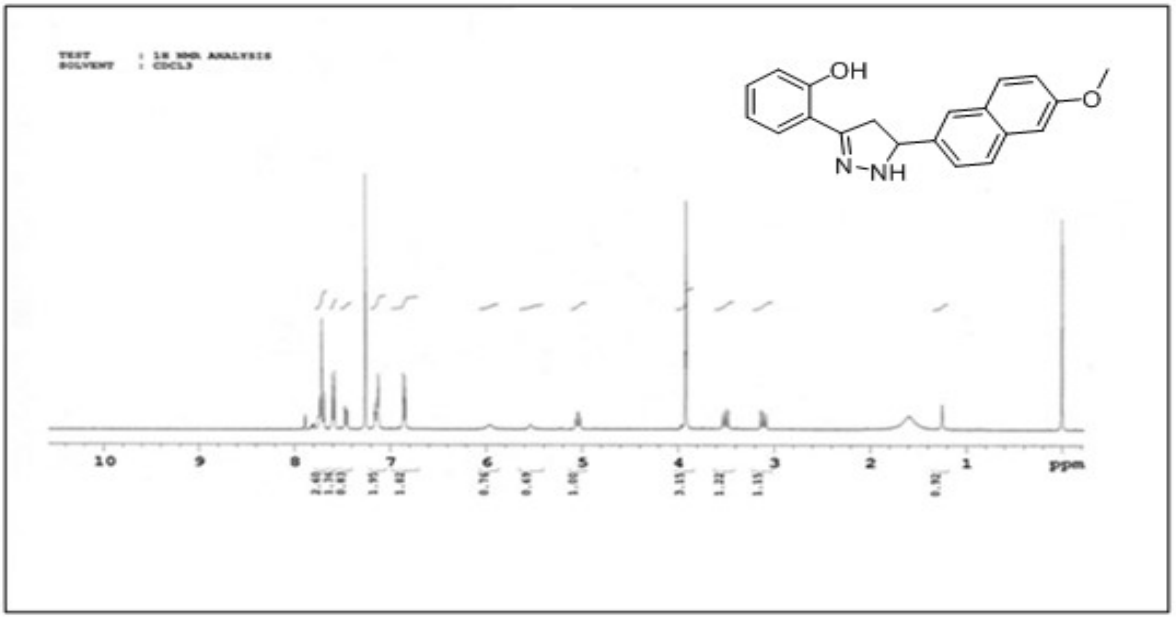
Figure 1



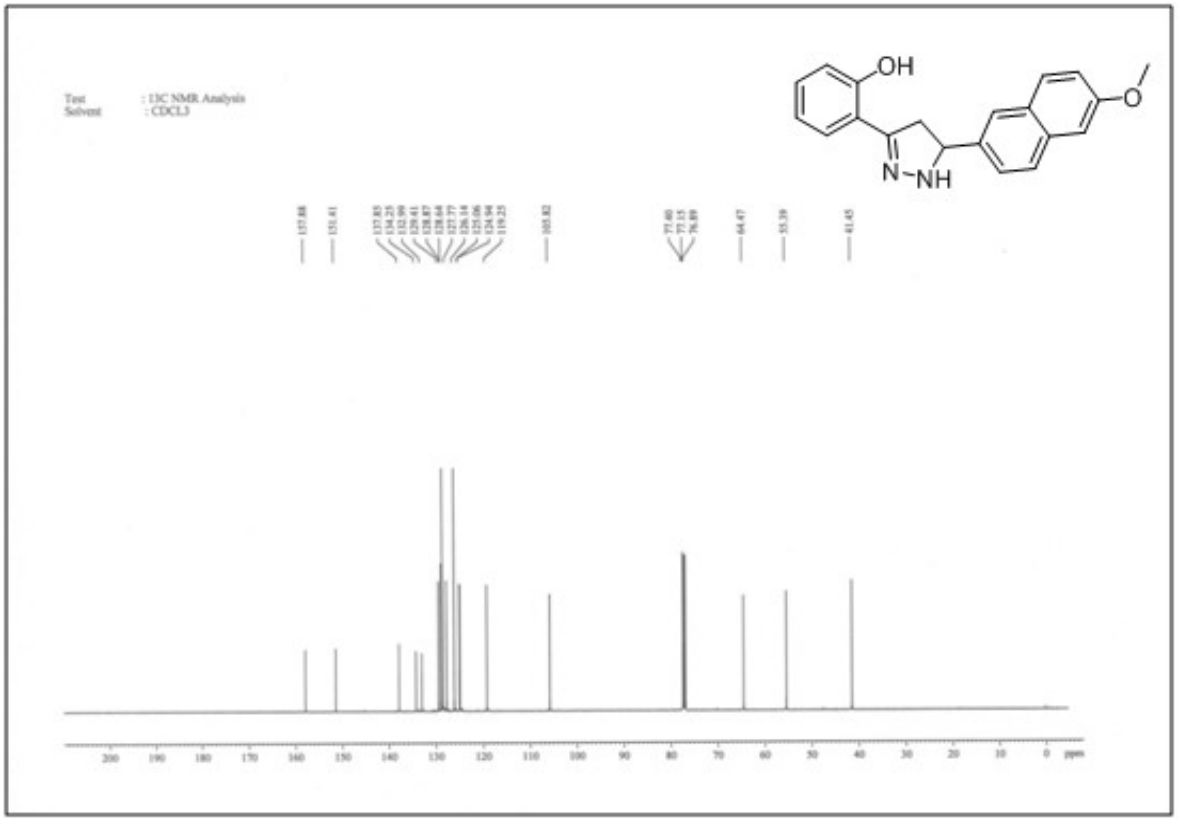
Spectrum 1: IR (KBr) cm^{-1} of M1B



Spectrum 2: Mass (m/z): 317 $[M+H]^+$ of M1B



Spectrum 3: ^{1}H NMR Spectrum of M1B



Spectrum 4: ^{13}C NMR Spectrum of M1B

Microbiological activity of the synthesized compounds:

In literature, the antimicrobial activity of pyrazoles, chromones, pyrazolines, chalcones, Schiff bases, ß-lactams, thiazolidinone etc. have shown that many of them are useful as bactericides and fungicides against various gram positive and gram negative bacteria and fungi **[20-22]**.

In the current work, some of the synthesized compounds were screened for *in-vitro* antibacterial activities against Gram +ve and Gram –ve bacteria. In Gram +ve bacteria, *Staphylococcus aureus* (*S. aureus*) and *Bacillus subtilis* (*B. subtilis*) were used and in gram –ve *Escherichia coli* (*E. coli*), *Pseudomona aeruginosa* (*P.aeruginosa)*) and *Salmonella abony (S. abony).* The activity of synthesized compound was compared by using Ciprofloxacin drug as comparator drug. On the other hand antifungal activity was also measured on above series of compounds against *Aspergillus niger* (*A. niger*) and *Candida albicans* (*C. albicans*) by using Fluconazole as standard and comparator drug.

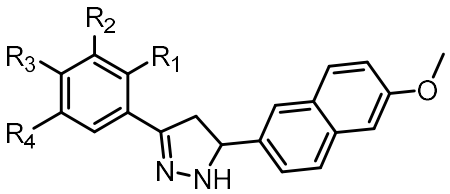
1. Test procedure for Antibacterial activity:

On each Petri plate containing 20mL of sterile Nutrient agar, 0.1mL of an authentic culture (corresponding to $5x10^{15}$ CFU/mL) of test organism was spread. Bore wells were bored on each plate and 30 microlitre of stock solution was added to it. This corresponds to concentration range of 30 microgram/mL of test compound. The tests were carried out in duplicate. Similarly, Ciprofloxacin concentration was added to the well as positive control, whereas Dimethyl sulphoxide (DMSO) solution was added as negative control to the wells **(Table 1)**.

2. Test procedure for Antifungal activity:

On each Petri plate containing 20 mL of sterile Saboraud's dextrose agar, 0.1mL of an authentic culture (corresponding to $5x10^{15}$ CFU/mL) of test organism was spread. Four bore wells were bored on each plate and 5 to 20 microlitre of stock solution was added to it. This corresponds to concentration range of 30 microgram/mL of test compound. The tests were carried out in duplicate. On the other hand, Fluconazole was added in same way as standard comparator and maintained as a positive control, whereas Dimethyl sulphoxide was added and maintained as a negative control **(Table 2)**.

Table 1: *In vitro* antimicrobial screening of M1B– M11B (Pyrazolines)

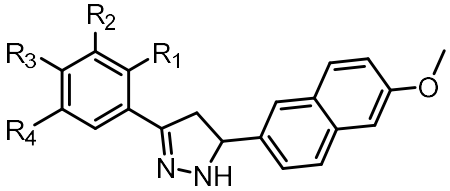


M1B-M9B

Compounds	R_1	R_2	R_3	R_4	Antibacterial zone of inhibition (in mm)			
					Microorganism			
					Gm+Ve		Gm-Ve	
					B. subtilis	*S. aureus*	*E. coli*	*P. aeruginosa*
M1B	**OH**	**H**	**H**	**H**	**07**	**08**	**12**	**07**
M2B	**H**	**H**	**OH**	**H**	**08**	**07**	**06**	**07**
M3B	**H**	**H**	**H**	**H**	**08**	**09**	**14**	**11**
M4B	**Cl**	**H**	**Cl**	**H**	**09**	**09**	**07**	**06**
M5B	**H**	**H**	**Cl**	**H**	**08**	**08**	**06**	**08**
M6B	**Cl**	**H**	**H**	**H**	**07**	**09**	**07**	**07**
M7B	**H**	**H**	**Br**	**H**	**08**	**05**	**06**	**06**
M8B	**C**	**H**	**CH_3**	**H**	**07**	**07**	**06**	**06**
M9B	**CH_3**	**H**	**H**	**H**	**07**	**07**	**07**	**09**
Control (Solvent)	**-**				**08**	**09**	**07**	**08**
Ciprofloxacin	**-**				**18**	**14**	**14**	**16**

Remarks: All compounds in series M1B-M9B showed inferior antibacterial activity as compared to the standard drug Ciprofloxacin

Table 2: *In-vitro* antifungal screening of M1B– M11B (Pyrazolines)



M1B-M9B

Compounds	R_1	R_2	R_3	R_4	Antifungal zone of inhibition (in mm)	
					Microorganism	
					A. niger	*C. albicans*
M1B	**OH**	**H**	**H**	**H**	**05**	**08**
M2B	**H**	**H**	**OH**	**H**	**07**	**07**
M3B	**H**	**H**	**H**	**H**	**09**	**10**
M4B	**Cl**	**H**	**Cl**	**H**	**09**	**07**
M5B	**H**	**H**	**Cl**	**H**	**08**	**08**
M6B	**Cl**	**H**	**H**	**H**	**07**	**07**
M7B	**H**	**H**	**Br**	**H**	**09**	**07**
M8B	**C**	**H**	**CH_3**	**H**	**06**	**06**
M9B	**CH_3**	**H**	**H**	**H**	**06**	**06**
Control (Solvent)	**-**				**08**	**06**
Fluconazole	**-**				**13**	**12**

Remarks: All compounds in series M1B-M9B showed inferior antifungal activity as compared to the standard drug Fluconazole

CONCLUSIONS

- Alum (KAI $(SO_4)_2 \cdot 12H_2O$) as a catalyst provides an efficient methodology for the synthesis of different substituted Pyrazolines from various substituted Chalcones. The remarkable advantages offered by this method are the use of a stable and inexpensive catalyst, a simple procedure, mild reaction conditions and use of less toxic solvent ethanol for the crystallization.
- All compounds in series **M1B-M9B** showed inferior antibacterial and antifungal activity.

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