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BIOLOGICAL EVALUATION, SYNTHESIS AND CHARACTERIZATION OF SOME NOVEL MANNICH BASES OF PYRAZOLINE DERIVATIVES

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Keywords:

Chalcones, isonicotinohydrazide, 2-pyrazoline derivatives, Mannich Bases, Antibacterial, Antifungal activity

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ABSTRACT: In the present investigation, some novel Mannich Bases of Pyrazoline derivatives(7a-g) is synthesized by treating various substituted acetophenones (1a-g) with 6-methaoxy-1-napthaldehyde (2) in alcoholic sodium hydroxide to obtained intermediate Chalcones (3a-g), which was further treated with isonicotinohydrazide (4) to get (3-(4-substituted phenyl)-5-(6-methoxy naphthalen-1-yl)-4, 5-dihydro- 1H-pyrazol-1-yl) (pyridin-4-yl) methanone (5a-g). Further, it is refluxed for 6-10 h. with 4-chloroaniline (6) and formaldehyde in methanol to afford Mannich Bases *i.e.* (4-(((4-chlorophenyl) amino) methyl) -5-(6-methoxynaphthalen -1-yl)-3-substituted phenyl-4, 5-dihydro- 1H-pyrazol-1–yl)(pyridin-4-yl) methanone (7a-g). The structure of synthesized Mannich bases was confirmed on the basis of Spectral data (IR, 1H NMR, mass, and elemental analysis) and evaluated for the antimicrobial activity. The antimicrobial data revealed that the synthesized derivative possesses very promising to moderate antibacterial and antifungal activity.

INTRODUCTION: Among the wide variety of nitrogen-containing heterocycles that have been investigated for developing new therapeutic molecules, 2-pyrazoline and Mannich Bases attracted substantial attention of the medicinal chemists. The widespread use of 2-pyrazoline and Mannich Bases as scaffolds in medicinal chemistry establishes these moieties as an important bio-active class of heterocycles [1]. Pyrazoline signifies a key pioneered motif in heterocyclic chemistry and holds a major position in medicinal and pesticide chemistry due to its wide range of bioactivities such as antibacterial and antifungal [2, 3], anticonvulsant [4], anticancer [5], analgesic [6] and anti-inflammatory [7, 8].

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Mannich bases of heterocyclic molecules have been grabbing the attention of the synthetic chemists for their wide range of biological activities ranging from antibacterial [9], antifungal [10], anticancer [11], anticonvulsant [12] and anti–HIV [13]. Fascinated by various bioactivity of above-mentioned compounds along within corporate both these crucial functionalities in a single entity to exploit their collective medicinal potentials and pharmacophore approaches in drug discovery and design and in continuation of our work [14, 15] on the synthesis, biological activity and structure determination of various pyrazoline derivatives, we have planned to design and synthesize Mannich Bases of Pyrazoline derivatives, *i.e.* (4- (((4-chlorophenyl) amino) methyl) -5-(6- methoxynaphthalen-1- yl)-3-substitutedphenyl-4, 5-dihydro- 1H-pyrazol-1-yl) (pyridin-4-yl) methanone (7a-g).

MATERIALS AND METHODS:

Experimental: Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded using Perkin–Elmer spectrometer.

1H NMR spectra were recorded on Brucker Advance II 400 spectrometer in DMSO by using TMS as an internal standard. Thin layer chromate-graphy was performed with E. Merk pre-coated TLC plates, silica gel 60F254 with a thickness of 0.25 mm, and spots were visualized by irradiation with ultraviolet light (254 nm). Physical constants and analytical data of all the compounds reported in this paper.

General procedure for the synthesis of 1-(substituted phenyl)-3-(6-methoxynaphthalen-1-yl) prop-2-en- 1-one (Chalcone)[14] (3a-g): A mixture of substituted acetophenone (1a-g) (0.01 mol) and 6-methoxy-1-naphthaldehyde (2) (0.01 mol) was stirred in ethanol (30 ml) and then sodium hydroxide solution (15 ml, 0.02 mol) was added to it. The reaction mixture was kept overnight at room temperature, and then it was poured on crushed ice and acidified with dilute hydrochloric acid. The Chalcone *i.e.* [1-(substituted phenyl)-3-(6-methox-ynaphthalen-1-yl) prop-2-en-1-one] (3a-g) precipitate out as solid. Then it was filtered, dried, and purified by crystallization from acetic acid. Percentage yield and physical constants were recorded.

General procedure for the synthesis of` (3-(4-substituted phenyl)-5-(6-methoxy naphthalen-1-yl)-4, 5-dihydro- 1H-pyrazol -1-yl)(pyridin-4-yl) methanone14 (5a-g): A mixture of 1-(4-substituted phenyl) -3-(6-methoxynaphthalen- 1-yl) prop-2-en-1-one (3a-g) (0.01 mole) and isonicotinohydrazide (0.02 mole) in 50 mL ethanol was reflux for 6-8 h, excess ethanol was distilled and the resulting solution was kept overnight at room temperature and then it was poured on crushed ice, the precipitate of (3-(4-substituted phenyl) -5-(6 -methoxynaphthalen-1-yl)-4, 5-dihydro-1H-pyrazol-1-yl) (pyridin-4-yl) methanone (5a-g) separated out. Then it was filtered, dried and purified by crystallization from acetic acid. Percentage yield and physical constants were recorded.

General Procedure for Synthesis of Mannach bases (7a-g): In a clean & dry round bottom flask a solution of compounds (3- (4-substituted phenyl)-5-(6-methoxynaphthalen -1-yl)-4, 5-dihydro-1H-pyrazol-1-yl) (pyridin-4-yl) methanone (5a-g) (0.01 mol) in methanol (30 ml), formaldehyde (0.02 mol) and corresponding 4-chloroaniline (0.02 mol) were added.

The reaction mixture was refluxed for 6-10 h. The solvent was distilled off, and the residue was poured into ice water. The precipitated solid was filtered off, dried and recrystallized from ethanol. Percentage yield and physical constants were recorded

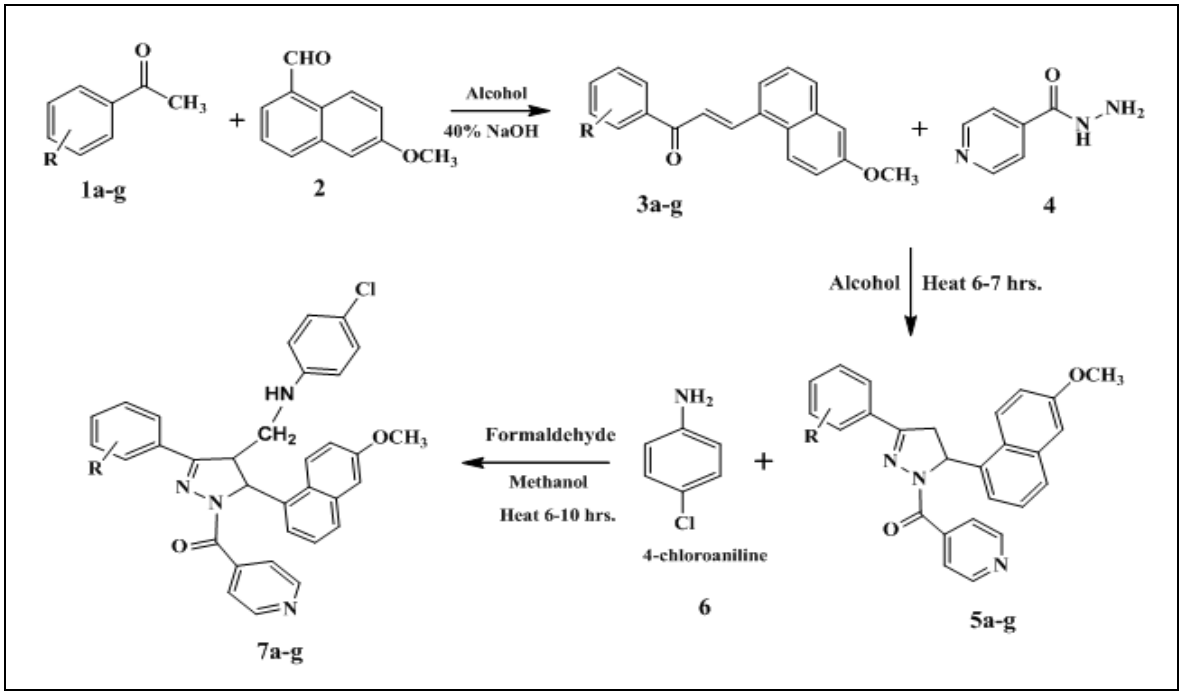

FIG. 1: (4-(((4-CHLOROPHENYL) AMINO) METHYL) -5- (6-METHOXYNAPHTHALEN-1-YL) -3-SUBSTITUTEDPHENYL-4, 5-DIHYDRO-1H-PYRAZOL-1-YL) (PYRIDIN-4-YL) METHANONE

RESULTS AND DISCUSSION: In the present investigation, some novel Mannich Bases of Pyrazoline derivatives (7a-g) is synthesized by treating various substituted acetophenones (1a-g) with 6-methaoxy-1-napthaldehyde (2) in alcoholic sodium hydroxide to obtained intermediate Chalcones (3a-g), which was further treated with isonicotinohydrazide (4) to get (3-(4-substituted phenyl)-5- (6-methoxy naphthalen-1-yl) -4, 5-dihydro-1H-pyrazol-1-yl) (pyridin-4-yl) methanone (5a-g). Further it is refluxed for 6-10 h. With 4-chloroaniline (6) and formaldehyde in methanol to afford Mannich Bases *i.e.* (4-(((4-chlorophenyl) amino) methyl)-5-(6-methoxynaphthalen-1-yl)-3-substitutedphenyl-4, 5-dihydro -1H-pyrazol-1-yl) (pyridin-4-yl) methanone(7a-g). Structure of synthesized Mannich bases was confirmed on the basis of Spectral data (IR, 1H NMR, mass and elemental analysis) and evaluated for the antimicrobial activity.

The analytical and spectral data is full agreement with the synthesized products. The IR spectrum of 7a-g exhibited an absorption peak at 3330 cm^{-1} due to (N-H), which is the absence in 6a-g. Further, in their 1H NMR (DMSO) spectrums, appearances of additional peaks at δ 6.57-6.42 ppm were assigned to CH_2 of Mannich base derivatives. The anti-microbial data revealed that the synthesized derivative possesses very promising to moderate antibacterial and antifungal activity.

Spectral Data of Compounds:

(7a):(4-(((4-chlorophenyl)amino)methyl)-5-(6-methoxynaphthalen-1-yl)-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl) (pyridin-4-yl) methanone: Yield: 85%, M.P. 165 °C, IR (KBr pellets cm^{-1}): N-H (3330), 3050 (Aromatic C-H streaching), Aliphatic C-H (2830), 1652 (>C=O), 1608 (C=N, pyrazoline ring), 1508 (C=C), 1154 (-OCH_3); 1H NMR (DMSO, 400 MHz) 8.65-8.45 (m, 6H, Ar-H),7.67-7.54(5H, m, Ar-H), 7.43-7.20 (4H, m, Ar-H), 6.93-6.77(4H, m, Ar-H), 6.57-6.42 (2H, d, CH_2), 5.28(1H, s, HN-Ar), 5.28-5.20(1H, d, -CH), 3.86 (s, 3H, OCH_3), 3.35-3.24(1H, m, -CH).; Mass (m/z): 547.05 (M+1).

(7b):(3- (4-chlorophenyl) -4-(((4-chlorophenyl) amino) methyl)-5-(6-methoxynaphthalen-1-yl)-4, 5- dihydro- 1H-pyrazol-1-yl) (pyridin-4-yl) methanone: Yield: 80%, M.P. 160 °C IR (KBr pellets cm^{-1}): N-H (3335), 3046 (Aromatic C-H streaching), Aliphatic C-H (2825), 1650 (>C=O), 1600 (C=N, pyrazoline ring), 1505 (C=C), 1150 (-OCH_3); 1H NMR (DMSO, 400 MHz) 8.63-8.42 (m, 6H, Ar-H), 7.64-7.52(4H, m, Ar-H), 7.40-7.30(4H, m, Ar-H), 6.90-6.67(4H, m, Ar-H), 6.55-6.40(2H, d, CH2), 5.25(1H, s, HN-Ar), 5.25-5.18(1H, d, -CH), 3.85(s, 3H, OCH_3), 3.32-3.20 (1H, m, -CH).; Mass (m/z): 580.14 (M+1).

(7c):(3- (4-bromophenyl) -4-(((4-chlorophenyl) amino)methyl)-5-(6-methoxynaphthalen-1-yl)-4, 5-dihydro -1H-pyrazol-1- yl)(pyridin-4-yl) methanone: Yield: 82%, M.P. 158 °C, IR (KBr pellets cm^{-1}): N-H (3325), 3045 (Aromatic C-H streaching), Aliphatic C-H (2820), 1650 (>C=O), 1600 (C=N, pyrazoline ring), 1505 (C=C), 1152 (-OCH_3); 1H NMR (DMSO, 400 MHz) 8.60-8.40 (m, 6H, Ar-H), 7.66-7.50 (4H, m, Ar-H), 7.40-7.18(4H, m, Ar-H), 6.90-6.60 (4H, m, Ar-H), 6.55-6.46(2H, d, CH2), 5.26 (1H, s, HN-Ar), 5.24-5.12(1H, d, -CH), 3.84 (s, 3H, OCH_3), 3.30-3.14(1H, m, -CH).; Mass (m/z): 624.09 (M+1).

7d):(4-(((4- chlorophenyl) amino) methyl)-3-(4-fluorophenyl) -5-(6-methoxynaphthalen-1-yl)-4, 5-dihydro -1H-pyrazol-1-yl) (pyridin-4-yl) methanone: Yield: 75%, M.P. 175 °C, IR (KBr pellets Cm-1): N-H (3320), 3042 (Aromatic C-H streaching), Aliphatic C-H (2826), 1645 (>C=O), 1610 (C=N, pyrazoline ring), 1518 (C=C), 1140 (-OCH_3); 1H NMR (DMSO, 400 MHz) 8.55-8.48 (m, 6H, Ar-H), 7.60-7.44 (4H, m, Ar-H), 7.43-7.20(4H, m, Ar-H), 6.90-6.67 (4H, m, Ar-H), 6.55-6.40(2H, d, CH2), 5.20(1H, s, HN-Ar), 5.28-5.20(1H, d, -CH), 3.82(s, 3H, OCH_3),3.30-3.14(1H, m, -CH).; Mass (m/z): 564.17 (M+1).

(7e):(4-(((4-chlorophenyl)amino)methyl)-5-(6-methoxynaphthalen -1-yl)-3- (p-tolyl)-4, 5-dihydro -1H-pyrazol -1-yl) (pyridin-4-yl) methanone: Yield: 85%, M. P. 155 °C, IR (KBr pellets cm^{-1}): N-H (3315), 3030 (Aromatic C-H streaching), Aliphatic C-H (2815), 1642 (>C=O), 1625 (C=N, pyrazoline ring), 1520 (C=C), 1134 (-OCH_3); 1H NMR (DMSO, 400 MHz) 8.61-8.42 (m, 6H, Ar-H), 7.61-7.50(4H, m, Ar-H), 7.40-7.10(4H, m, Ar-H), 6.88-6.55 (4H, m, Ar-H), 6.60-6.40(2H, d, CH_2), 5.25(1H, s, HN-Ar), 5.20-5.10(1H, d, -CH), 3.75(s, 3H, OCH_3), 3.36-3.24(1H, m, -CH), 2.73(s, 3H, -CH_3); Mass (m/z): 560.20 (M+1).

(7f):(4-(((4- chlorophenyl) amino) methyl)-5-(6-methoxynaphthalen -1-yl) -3-(4- methoxy-phenyl)-4, 5-dihydro -1H-pyrazol-1-yl) (pyridin-4-yl) methanone: Yield: 72%, M.P. 170 °C, IR (KBr pellets Cm^{-1}): N-H (3310), 3020 (Aromatic C-H streaching), Aliphatic C-H (2810), 1632 (>C=O), 1638 (C=N, pyrazoline ring), 1528 (C=C), 1154 (-OCH_3); 1H NMR (DMSO, 400 MHz) 8.62-8.48 (m, 6H, Ar-H), 7.61-7.54 (4H, m, Ar-H), 7.40-7.23(4H, m, Ar-H), 6.90-6.72 (4H, m, Ar-H), 6.57-6.42(2H, d, CH_2), 5.20(1H, s, HN-Ar), 5.18-5.09(1H, d, -CH), 3.86 (s, 3H, OCH_3), 3.86(s, 3H, OCH_3), 3.30-3.14(1H, m, -CH).; Mass (m/z): 576.19 (M+1).

(7g):(4-(((4- chlorophenyl)amino)methyl)-3-(2,4-dichlorophenyl)-5- (6-methoxynaphthalen-1-yl)-4, 5-dihydro- 1H-pyrazol-1-yl) (pyridin-4-yl) methanone: Yield: 65%, M.P. 163 °C, IR (KBr pellets cm^{-1}): N-H (3320), 3052 (Aromatic C-H streaching), Aliphatic C-H (2830), 1642 (>C=O), 1608 (C=N, pyrazoline ring), 1538 (C=C), 1144 (-OCH_3); 1H NMR (DMSO, 400 MHz) 8.61-8.47 (m, 6H, Ar-H), 7.64-7.54(4H, m, Ar-H), 7.33-7.20(3H, m, Ar-H), 6.93-6.67 (4H, m, Ar-H), 6.54-6.42(2H, d, CH2), 5.26(1H, s, HN-Ar), 5.28-5.20(1H, d, -CH), 3.82(s, 3H, OCH_3), 3.31-3.21 (1H, m, -CH).; Mass (m/z): 614.10 (M+1).

Biological Activity: The newly synthesized Mannich Bases derivatives were screened for their antibacterial activity against *E. coli*, *Salmonella typhi*, *Staphylococcus aureus* and Bacillus subtilis by disc diffusion method [16, 17] using penicillin as standard and antifungal activity against *Aspergillus niger*, *Aspergillus flavus*, *Penicillium chrysogenum*, *Fusarium moneliforme*, by poison plate method [18] using Griseofulvin as the reference standard and DMSO as control solvent. From antibacterial screening results, it indicates that some of the compounds show significant antibacterial property and some of the compounds are moderately activity. The data of antifungal activity revealed that some Mannich Basis derivatives possess promising, and some compounds show no antifungal activity. The results are shown in **Table 1** and **2,** respectively.

TABLE I: ANTIBACTERIAL SCREENING RESULTS OF THE COMPOUNDS 7a-g

S. no.	Entry	Diameter of growth inhibition zone (mm)			
		E. coli	*Salmonella typhi*	*Staphylococcus aureus*	*Bacillus subtilis*
1	7a	08	12	15	11
2	7b	17	20	24	19
3	7c	16	20	14	1
4	7d	24	22	14	17
5	7e	09	10	13	13
6	7f	19	16	17	18
7	7g	13	10	13	15
8	DMSO	-ve	-ve	-ve	-ve
9	Penicillin	22	25	35	38

-ve no antibacterial activity

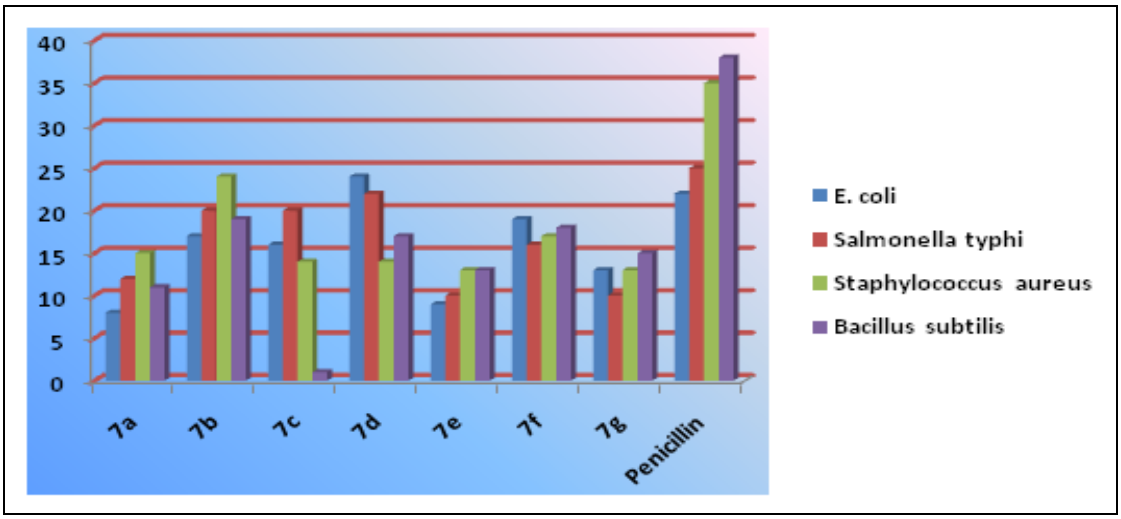

FIG. 2: FLOW CHART FOR ANTIBACTERIAL SCREENING

TABLE 2: ANTIFUNGAL SCREENING RESULTS OF THE COMPOUNDS 7a-g

S. no.	Entry	Diameter of growth inhibition zone (mm)			
		Asp. Niger	***Asp. flavus***	***Pen. chrysogenum***	***Fusarium Moneliforme***
1	7a	-ve	-ve	+ve	RG
2	7b	+ve	-ve	-ve	-ve
3	7c	-ve	-ve	-ve	RG
4	7d	-ve	+ve	-ve	-ve
5	7e	-ve	RG	+ve	+ve
6	7f	-ve	-ve	-ve	-ve
7	7g	-ve	-ve	-ve	-ve
8	DMSO	+ve	+ve	+ve	+ve
9	Griseofulvin	-ve	-ve	-ve	-ve

-ve -No growth Antifungal activity present , +ve -Growth Antifungal activity absent RG -Reduced growth

CONCLUSION: In the above paper, we have synthesized some novel Mannich Bases of Pyrazoline Derivatives and evaluate for anti-bacterial and antifungal activities. From the antimicrobial data, it can be concluded that test compounds 7b, 7c, 7d, and 7f were found to possess moderate antibacterial activity against gram-positive bacteria and gram-negative bacteria compared with Penicillin and also possesses very good to moderate antifungal activity.

From the above results, it suggested that Mannich bases of appropriately substituted Pyrazoline have good potential for further development as antimicrobial agents, which help to the modern chemist who is working under this area.

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CONFLICTS OF INTEREST: The author declares no conflict of interest.

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