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Synthetic aspects for some novel pyrazolines and their evaluation as antimicrobial agent

S. Shah N. N, Hanfi M. Ziauddin and M. A. Baseer*

P.G. Department of Chemistry, Yeshwant College Nanded (India)

ABSTRACT

With the persuasion to synthesize the molecules of biological interest we reported here the synthesis of pyrazolines from pyrrolidine chalcones and phenyl hydrazine under basic condition using methanol as a solvent media. These synthesized molecules were characterized by chemical and spectral analysis (IR, ^{1}HNMR and mass) data. And the biological activities of these compounds were tested against different strains of bacteria and some of the fungi. As a result we got good to moderate activity which on further derivatization and modifications can provide us new route for the bioactive molecules.

Key words: Chalcones, Phenyl hydrazine, Pyrazolines, Antimicrobial activity.

INTRODUCTION

Pyrazolines are the five member heterocycles containing two nitrogen atoms. A glance at the previous research indicates the supremacy of pyrazolines as biologically potent molecules on other heterocycles[1-5]. With the emergence of various diseases, the duties of a chemist are acquiring more responsibilities. Most of the infectious diseases are chasing for the ranks. Tuberculosis (TB) considered as a number one killer producing over two million casualties annually worldwide[13], *Helicobacter pylori* is supposed to be clause I carcinogen in humans as suggested by WHO (World Health Organization)[6] & in addition to this a well known disease malaria accounts three million deaths annually and every 30s an African child killed by malaria, reported by WHO[7].

Such dreadful diseases accounting for the high mortality rates encouraged us to put forth the molecules which can be established as potent drug for such diseases. Literature shows that pyrazolines are responsible for variety of biological applications such as insecticidal [8],

antitumor[9], antidepressant[10], antimycobacterial[11], antihistaminic[12], anticoagulant [13] and others[14-21].

In recent years, pyrazoline unit attached with flourene-carbazole–based polymers provided the properties such as better thermal stability, higher photoluminescence quantum efficiency and film forming property hence could be used as light emitting material[22].

MATERIALS AND METHODS

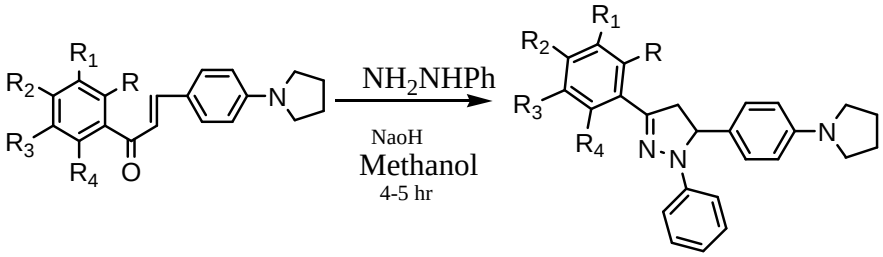
Experimental

All the melting points were determined in open capillary method and are uncorrected. IR spectra were recorded as a KBr pellets on Perkin-Elmer FT IR 240-c spectrometer. ^{1}HNMR spectra on a Bruker Avance DPX400 MHz spectrometer with $CDCl_3$ as a solvent and TMS internal standard. The chemical shift values are expressed in part per million (ppm) downfield from the internal standard and signals are quoted as s (singlet), d (doublet), t (triplet) and m (multiplate). Purity of the compounds is checked by TLC plates (Merck) using benzene and ethyl acetate as an eluent in the ratio of (7:3 v/v).

Synthetic procedure for pyrazolines:

Pyrrolidine chalcone (2 mmol) and phenyl hydrazine (2 mmol) were dissolved in methanol (15 ml). To this solution sodium hydroxide (2.5 mmol) was added and the reaction mixture was refluxed for few hours. The progress of the reaction is monitored by TLC. After accomplishment of the reaction, distillation was carried out to remove excess of solvent and the remaining mass poured into crushed ice. The obtained solid was washed with water and recrystalised by using methanol.

Physical data of all the newly synthesized compounds mentioned in **table1**.



(I-XI)

Entry	R	R_1	R_2	R_3	R_4
I	H	H	H	H	H
II	H	H	OCH_3	H	H
III	H	F	OCH_3	H	H
IV	OCH_3	H	H	OCH_3	H
V	H	H	OH	H	H
VI	OH	H	H	H	H
VII	OH	H	H	Cl	H
VIII	OH	I	H	Cl	H
IX	OH	H	CH_3	Cl	H
X	OH	Cl	H	Cl	H
XI	OH	H	CH_3	H	H

Scheme I : Synthesis of Phenyl Pyrazolines

RESULTS AND DISCUSSION

We are here with some novel pyrazolines which are synthesized by refluxing pyrrolidine chalcones with phenyl hydrazine in presence of base. Methanol was used as solvent for the reaction, TLC provided us the preliminary base for accomplishment of the reaction. These synthesized compounds were evaluated for their antimicrobial activity and the results showed moderate to good activity against different gram positive and negative bacteria and fungi.

Spectroscopic data of synthesized compounds:

1,3-Diphenyl-5-(4-pyrrolidin-1-yl-phenyl)-4,5-dihydro-1H-pyrazole(I):

IR(KBr): 1600cm^{-1}(C=N), 1159cm^{-1}(C-N); **^{1}HNMR:** δ 1.9 (t,4H,CH_2), δ 3.0(dd, 1H, H_a), δ 3.15 (t,4H,CH_2), δ 3.8(dd, 1H, H_b), δ 5.3 (dd, 1H ,H_x), δ 6.7-7.8 (m,14H,Ar-H); **M.S. (m/z):** m+1= 368.2

3-(4-Methoxy-phenyl)-1-phenyl-5-(4-pyrrolidin-1-yl-phenyl)-4,5-dihydro-1H-pyrazole (II)

IR(KBr): 1605cm^{-1}(C=N), 1152cm^{-1}(C-N); **^{1}HNMR:** δ 1.9 (t,4H,CH_2), δ 3.1(dd, 1H, H_a), δ 3.2 (t,4H,CH_2), δ 3.7(dd, 1H, H_b), δ 3.8 (s,3H,OCH_3), δ 5.4 (dd, 1H ,H_x), δ 6.8-7.7 (m,13H,Ar-H); **M.S. (m/z):** m+1= 398.2

3-(3-Fluoro-4-methoxy-phenyl)-1-phenyl-5-(4-pyrrolidin-1-yl-phenyl)-4,5-dihydro-1H-pyrazole(III)

IR(KBr): 1606cm^{-1}(C=N), 1157cm^{-1}(C-N); **^{1}HNMR:** δ 1.9 (t,4H,CH_2), δ 3.0(dd, 1H, H_a), δ 3.15 (t,4H,CH_2), δ 3.6(dd, 1H, H_b), δ 3.8 (s,3H,OCH_3), δ 5.2 (dd, 1H ,H_x), δ 6.9-7.8 (m,12H,Ar-H); **M.S. (m/z):** m+1= 416.2

Table1. Physical data of synthesized compounds (I-XI)

Entry	Molecular formula	Yield (%)	Melting point (°C)
I	$C_{25}H_{25}N_3$	88	143
II	$C_{26}H_{27}N_3O$	80	165
III	$C_{26}H_{26}FN_3O$	81	178
IV	$C_{27}H_{29}N_3O_2$	88	185
V	$C_{25}H_{25}N_3O$	84	225
VI	$C_{25}H_{25}N_3O$	90	196
VII	$C_{25}H_{24}ClN_3O$	87	125
VIII	$C_{25}H_{23}ClIN_3O$	78	205
IX	$C_{26}H_{26}ClN_3O$	83	285
X	$C_{25}H_{23}Cl_2N_3O$	88	260
XI	$C_{26}H_{27}N_3O$	82	203

Antimicrobial activity

Antimicrobial screening was done by using cup plate method [23-24] at a concentration of 100µg/ml. All compounds were checked for their in vitro antimicrobial activity against different strains of bacterias and mentioned fungi as described in table 2. DMSO was used as solvent control. These synthesized compounds were found to exhibit moderate to good activity.

Table 2: Antimicrobial activity of synthesized compounds (I-XI)

Products	Bacteria (Zone of Inhibition in mm)				Fungi (Zone of Inhibition in mm)			
	A	B	C	D	E	F	G	H
I	14	---	24	21	---	---	---	---
II	16	13	12	08	---	---	---	---
III	13	---	11	---	12	---	---	---
IV	10	15	22	12	---	---	---	---
V	15	13	17	---	22	---	---	---
VI	---	10	11	11	21	---	---	---
VII	09	12	12	13	24	---	---	---
VIII	25	26	16	21	31	---	---	---
IX	17	12	12	13	17	---	---	---
X	---	---	11	15	25	---	---	---
XI	13	12	15	13	17	---	---	---

A= Bacillus subtilis gr +ve, B= Pseudomonas aeruginosa gr –ve,C= Staphylococcus aureusgr +ve, D= Escherichia coli gr –ve, E= Aspergillus niger,F= Aspergillus Flavus, G= Curvularia H=Alternaria

CONCLUSION

We have synthesized some novel pyrazolines using pyrrolidine chalcones and phenyl hydrazine under basic condition. These synthesized molecules were characterized by chemical and spectral analysis data and are further subjected to antimicrobial activity which provided us moderate to good activity. The utilized pyrrolidine chalcones possess different pharmacophores on the ketone ring which are responsible for the variety of biological and medicinal activities as concluded by the literature. In addition to this presence of pyrrlolidine ring is the key support for the biological importance of synthesized pyrazolines. Here we reported only antimicrobial activity with limited bacteria and fungi which shows moderate to good activity but these on derivatization and some modifications in the pharmacophoric substitutions would yield striking pharmacological activities which will be explored in our future studies.

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