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Research Article

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Synthesis and characterization of some novel pyrazolines as antimicrobial agents

Dhaval C. Manvar* and Jaysukhlal M. Parmar

Department of Chemistry, Maharaja Mahendrasinhji Science College, Morbi, Affiliated to Saurashtra University, Gujarat, India

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ABSTRACT

*1-{4-[(4-nitrobenzyl)oxy]phenyl}ethanone **3** was prepared by condensation 4-hydroxy acetophenone **1** 4-nitro benzyl bromide **2** in acetonitrile. The reaction of **3** with various aromatic aldehyde to give chalcones **4** which on reaction with hydrazine hydrate in catalytic amount of glacial acetic acid to give Pyrazolines **5.** The newly synthesized compounds have been characterized by IR, ^{1}H NMR, MASS Spectra. The synthesized compounds were screened for antimicrobial activity. The purity of synthesized compound was confirmed by TLC.*

Key words: Pyrazolines, chalcones, claisen-Schimdt condensation, Antimicrobial activity

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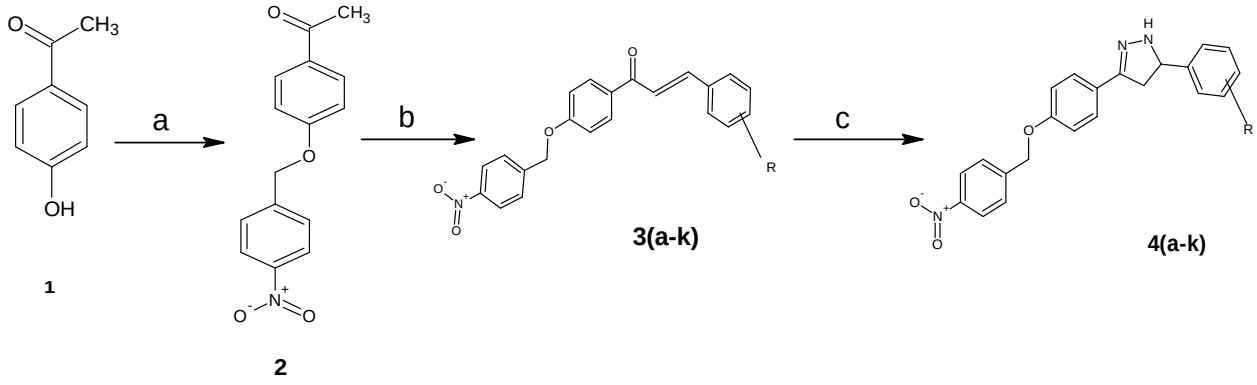
INTRODUCTION

Chalcones are natural substances found in a number of plants or synthetically prepared. These compounds are of a high interest due to their use as a starting materials in the synthesis of a series of heterocyclic compounds[1-4]. Nitrogen containing five membered heterocyclic compounds, natural as well as synthetic, have received considerable attention due to the wide range of pharmacological activities. Various substituted Pyrazolines and their derivatives are important biological agent and a significant amount of research activity has been directed towards this class of compounds. In particular, they show antimicrobial[5-8], Antimicobactirial[9], anti-inflammatory, and analgesic[10-12] and antidepressant activities[13]. In view of these observations and in continuation of the research work on bioactive heterocycles[14-16]. It was intended to design and synthesize some new Pyrazolines derivatives and evaluated them for antimicrobial activities.

EXPERIMENTAL SECTION

Melting points were determined in open capillary tubes in a Thomas Hoover melting point apparatus and are uncorrected. The purity of the compounds was confirmed by thin layer chromatography. The spots were developed in iodine chamber and visualized under ultraviolet lamp. Infrared (IR) and ^{1}H nuclear magnetic resonance (^{1}H NMR) spectra were recorded for the compounds in SHIMADZU FTIR 8400 Spectrophotometer and BRUKER Spectrometer (400 MHz) respectively. Chemical shift are reported in parts per million (PPM) using tetramethylsilane (TMS) as an internal standard.



Scheme 1. Reagents and conditions: (a) p-nitrobenzyl bromide, Anhydrous K_2CO_3, acetonitrile, reflux, 12-15 hr. (b) substituted aromatic aldehyde, KOH, methanol, at rt 24-30 hrs (c) Hydrazine hydrate, n-butanol, reflux 24 hrs

Procedure for Synthesis of 1-{4-[(4-nitrobenzyl)oxy]phenyl}ethanone (2):
A mixture of p-hydroxy acetophenone (0.01mole) (1), anhy. Potassium carbonate(0.015 mole), and p-nitro benzyl bromide(0.01 mole) in 30 ml acetonitrile was refluxed for 12-15 hr. completion of reaction was checked by TLC using mobile phase ethylene dichloride/ethyl acetate(8/2).The reaction mixture was then cool to rt and dump in crushed ice. Filtered ppt and digested in 5% NaOH solution and crystallized from methanol.

Characterization of 1-{4-[(4-nitrobenzyl)oxy]phenyl}ethanone (2):
Yellow crystal, mp230-232 ^{0}C, 1H NMR (DMSO-d6) δ ppm: 2.42(s, 3H), 5.04(s, 2H), 6.82(d, 2H), 7.39(d, 2H), 7 .80(d, 2H), 8.02(d, 2H). IR(cm^{-1}): 3081 (Aromatic C-H Str.), 1523 (Aromatic C=C Str.), 2944 (Alkane assy. Str.), 1670 (>C=O Str.), 1248 (ether C-O-C). MS: 272 (M+1). Yield 81 %.

Procedure for Synthesis of 1-{4-[(4-nitrobenzyl)oxy]phenyl}-3-phenylprop-2-en-1-one (3a-k):
A mixture of **2** (0.01 mole), KOH (0.015 mole) and substituted aromatic aldehyde(0.01 mole) in methanol stirring at RT. The compilation of reaction was monitored by TLC. After complication of reaction, the contents were poured into ice cold water and neutralized with dil. HCL. Yellow solid obtained was filtered, dried and purified by recrystallization from DMF- methanol. The physical data were recorded in Table No. I.

Characterization of 1-{4-[(4-nitrobenzyl)oxy]phenyl}-3-phenylprop-2-en-1-one(3a):
Yellow crystal mp. 168-170 ^{0}C, ^{1}H NMR (DMSO-d6) δ ppm: 8.30 (d, 2H), 8.21 (d, 2H), 7.98(d, 1H), 7.90 (d, 2H), 7.88 (d, 2H), 7.77 (d, 1H), 7.74 (m, 3H), 7.21 (d, 2H), 5.43 (s, 2H). IR(cm^{-1}): 3076 (Aromatic C-H Str.), 1513(Aromatic C=C Str.), 2899(Alkene ass, str.), 1654 (>C=O Str.), 1605 (-C=C-), 1261 (ether C-O-C). MS: 360 (M+1). Yield 85%

Procedure for Synthesis of 3-{4-[(4-nitrobenzyl)oxy]phenyl}-5-phenyl-4,5-dihydro-1H-pyrazole(4a-k).
A mixture of **(3a-k)** (0.01 mole), hydrazine hydrate (0.015 mole) in 20 ml n-butanol was refluxed. Completion of reaction was monitored by TLC using mobile phase ethylene dichloride/ethyl acetate (8:2). The reaction mixture was then kept at RT over night. Precipitated product was filtered off and crystallized from DMF- methanol. The physical data were recorded in Table No. I.

Characterization of 3-{4-[(4-nitrobenzyl)oxy]phenyl}-5-phenyl-4,5-dihydro-1H-pyrazole(4a).
Light yellow crystal, mp. 151-153^{0}C, ^{1}H NMR (DMSO-d6) δ ppm:8.26 (d, 2H), 7.72(d, 2H), 7.58(d, 2H), 7.37(m, 4H), 7.27(t, 3H), 7.05(d, 2H), 5.29(s, 2H), 4.81(t, 1H), 3.44(dd, 1H), 2.82(dd, 1H). IR(cm^{-1}): 3325 (NH- str.), 1516(- C=N str.), 1253 (ether C-O-C). MS. 374(M+1) yield 69%.

RESULTS AND DISCUSSION

Antibacterial activity
The minimum inhibitory concentrations (MICs) of the tested compounds are shown in table 2. The different compounds 4(a-k) where tested for in vitro against 2 gram positive (Staphylococcus aureus & Bacillus megaterium) and 2 gram negative (Escherichia coli & Pseudomonas aeruginosa) bacteria. From the screening data, most of the compounds possessed very good antibacterial activity. Compounds **4b, 4c, 4g, 4i** and **4j** showed MBC value 250 µg/ml while ampicillin has standard MBC value of 100 µg/ml against gram positive *S. aureus.* Compounds **4b, 4c, 4e, 4g, 4i** and **4j** showed MBC value in the range between

250-500 µg/ml which indicates very good activity against gram positive *B. megaterium.* Compound **4c, 4g, 4i** showed MBC value in the range of 250 µg/ml while Streptomycin has standard MBC value of 50 µg/ml against gram negative *E. Coli* which indicates that this compounds have moderate activity. The remaining pyrazoline derivatives possessed moderate to poor activity against all four bacterial spices.

Antifungal activity

The minimum inhibitory concentrations (MICs) of the synthesized compounds are shown in Table 2. For in vitro antifungal activity, two fungal species *A. flavus* and *A. niger*. Most of the compounds possessed very good antifungal activity against *A. niger*; their MFC values were in the range between 250- 500 µg/ml. Compounds 4c and 4g showed excellent activity of 250 µg/ml; 4b, 4h and 4j possessed very good activity of 500 µg/ml against *A. niger.* whereas remaining compounds possessed moderate to poor activity against *A. niger* and *A. flavus* compared with Nystatin.

Table 1 : Physical constants of the title compounds 3a-k and 4a-k

Comp. ID	Molecular Formula	Mol.wt.	R	Yield %	m.p. °C
3a	$C_{22}H_{17}NO_4$	359	H	85	168-170
3b	$C_{22}H_{16}ClNO_4$	394	4-Cl	77	156-157
3c	$C_{23}H_{19}NO_5$	389	4-OMe	70	142-144
3d	$C_{22}H_{16}BrNO_4$	438	4-Br	65	171-173
3e	$C_{22}H_{17}NO_5$	375	4-OH	62	180-182
3f	$C_{22}H_{17}NO_5$	375	3-OH	58	175-177
3g	$C_{23}H_{19}NO_5$	389	3-OMe	64	157-159
3h	$C_{22}H_{16}ClNO_4$	394	3-Cl	60	138-140
3i	$C_{23}H_{19}NO_5$	389	2-OMe	80	171-173
3j	$C_{24}H_{21}NO_6$	419	3,4-OMe	78	185-187
3k	$C_{22}H_{16}N_2O_6$	404	3-NO_2	60	252-255
4a	$C_{22}H_{19}N_3O_3$	373	H	75	154-156
4b	$C_{22}H_{18}ClN_3O_3$	408	4-Cl	78	146-148
4c	$C_{23}H_{21}N_3O_3$	403	4-OMe	80	191-194
4d	$C_{22}H_{18}BrN_3O_3$	452	4-Br	72	200-202
4e	$C_{22}H_{19}N_3O_4$	389	4-OH	61	205-207
4f	$C_{22}H_{19}N_3O_4$	389	3-OH	63	223-225
4g	$C_{23}H_{21}N_3O_4$	403	3-OMe	66	168-170
4h	$C_{22}H_{18}ClN_3O_3$	408	3-Cl	68	191-193
4i	$C_{23}H_{21}N_3O_4$	403	2-OMe	62	159-161
4j	$C_{24}H_{23}N_3O_5$	433	3,4-OMe	70	177-179
4k	$C_{22}H_{18}N_4O_5$	418	3-NO_2	61	220-222

Table 2 : Antimicrobial and antifungal data of compounds 4a-k

Comp. ID	Minimal bactericidal concentration µg/ml				Minimal fungicidal concentration µg/ml	
	Gram negative		Gram positive			
	E. Coli	*P. aeruginosa*	*S. aureus*	*B.megaterium*	*A. flavus*	*A. niger*
4a	1000	1000	1000	1000	1000	1000
4b	1000	500	250	500	500	500
4c	250	500	250	250	500	250
4d	1000	500	1000	1000	1000	1000
4e	1000	1000	1000	500	1000	1000
4f	1000	1000	1000	1000	1000	1000
4g	250	500	250	500	250	250
4h	500	500	500	1000	1000	500
4i	250	500	250	250	500	1000
4j	500	1000	250	500	500	500
4k	1000	500	1000	1000	1000	1000
Streptomycin	50	50	-	-	-	-
Ampicillin	-	-	100	100	-	-
Nystatin	-	-	-	-	100	100

CONCLUSION

Experimental work was started from the Claisen-Schimdt condensation of 1-{4-[(4-nitrobenzyl)oxy]phenyl}ethanone **2** with substituted aldehyde to give corresponding 1-{4-[(4-nitrobenzyl)oxy]phenyl}-3-arylprop-2-en-1-one **3a-k** in methanolic solution of potassium hydroxide at rt. The reaction of 1-{4-[(4-nitrobenzyl)oxy]phenyl}-3-arylprop-2-en-1-one **3a-k** with hydrazine hydrate in n-butanol to give 3-{4-[(4-nitrobenzyl)oxy]phenyl}-5-phenyl-4,5-dihydro-1H-pyrazole **4a-k** in fairly good yield.

Synthesized compounds **4a-k** were evaluated for their antibacterial activities against different strain of bacteria and we conclude that the some newly synthesized compounds displayed excellent antibacterial and antifungal activity.

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