WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 7.523
Volume 6, Issue 9, 809-814. Research Article ISSN 2277– 7105

SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL ACTIVITY OF A SERIES OF METHYL BENZYLOXY PYRAZOLINE DERIVATIVES USING ALKALI AS CATALYTIC AGENTS

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Article Received on
30 June 2017,
Revised on 20 July 2017,
Accepted on 10 August 2017
DOI: 10.20959/wjpr20179-9261

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ABSTRACT

Some new 3-Aryl-5-[4'-(p-methylbenzyloxy)-3'-methoxyphenyl]-4,-5-dihydro-1H-pyrazoles **(1a-l)** and 3-Aryl-1-carbothioamide-5-[4'-(p-methylbenzyloxy)-3'-methoxyphenyl]-4,-5-dihydro-1H-pyrazoles **(2a-l)** were prepared. All the prepared compounds were characterized by their spectral (I.R., N.M.R., Mass) data and screened for their antimicrobial activities.

KEYWORDS: Chalcone, Pyrazoline, Carbothioamide, Antimicrobial activities.

INTRODUCTION

Pyrazoline derivative[1-6] have been found to possess wide range of therapeutic activity such as antidiabetic[7], antiimplantation[8], antiallergic[9], anticonvulsant[10-11], antineoplastic[12], anti-inflammatory[13], antitumor[14], analgesic[15-16] antimicrobial[17], bactericidal[18-19] etc. Pyrazolines and Carbothioamide have proved to be the most useful framework for biological activities, Both have attracted attention of medicinal chemists for both with regard to heterocyclic chemistry and the pharmacological activities associated with them. This inspired us to synthesize 3-Aryl-5-[4'-(p-methylbenzyloxy)-3'-methoxyphenyl]-4,-5-dihydro-1H-pyrazoles **(1a-l)** and 3-Aryl-1-carbothioamide-5-[4'-(p-methylbenzyloxy)-3'-methoxyphenyl]-4,-5-dihydro-1H-pyrazoles **(2a-l).**

The structure of synthesized compounds were assigned based on Elemental analysis, I.R. ^{1}H-NMR and Mass spectral data. The antimicrobial activity was assayed by using the cup-plate agar diffusion method[20] by measuring the zone of inhibition in mm. All the compounds were screened *in vitro* for their antimicrobial activities[21] against varieties of bacterial strains such

Staphylococcus aureus, *Bacillus subtillis*, *Escherichia coli*, Proteus vulgaris and fungi *Aspergillus niger* at 40µg concentration. Standard drugs like Ampicillin, Amoxicillin, Norfloxacin, Benzyl penicillin and Griseofulvin were used for comparison purpose (Table-1).

RESULTS AND DISCUSSION

The synthesis of 1-Aryl-3-[4'-(o-chlorobenzyloxy)-3'-methoxyphenyl]-propenones (1a-l) and 3-Aryl-5-[4'-(o-chlorobenzyloxy)-3'-methoxyphenyl]-4,-5-dihydro-1H-pyrazoles (2a-l) was carried out in two steps, first by the condensation of 4-[(2-chlorobenzyl)oxy]-3-methoxy benzaldehyde (1) with different aromatic acetophenone by Claisen-shmidt condensation in presence base catalyst to give chalcone derivatives (1a-l), which in next step were refluxed with hydrazine hydrate to yield pyrazoline derivatives (2a-l). (scheme-1).

The formulas of the selected compounds were confirmed by the elemental analysis and their structures were determined by IR,[1] H-NMR, and mass spectral data.

ANTIBACTERIAL ACTIVITY

It has been observed from the microbiological data that all compounds (1a-l) and (2a-l) were found to be mild to moderately active against Gram positive and Gram negative bacterial strains.

ANTIFUNGAL ACTIVITY

The antifungal data revealed that compounds were least toxic to the fungal strain. However mild activity was shown by the compounds against **A.niger.** The antibacterial activity was compared with standard drug viz. and antifungal activity was compared with standard drug viz. Griseofulvin.

EXPERIMENTAL SECTION

Melting points were taken in open capillary tubes are uncorrected. IR spectra (cm^{-1}) were recorded on Shimadzu-435-IR Spectrophotometer and, ^{1}H-NMR spectra on Bruker spectrometer (300MHz) using TMS as an internal standard, chemical shift in δ ppm.

General procedure for the preparation of 1-Aryl-3-[4'-(p-methylbenzyloxy)-3'-methoxyphenyl]-propenones

Take a mixture of 4-[(p-methylbenzyl)oxy]-3-methoxy benzaldehyde (1) (0.01M) and 4-methoxy aceto phenone (0.01) in methanol, add a NaOH (0.002M) to the reaction mixture . The reaction mixture was magnetically stirred for 12 hrs and then left overnight. After it was

pour over ice and neutralised with dil.HCl and ethanol is added for crystallisation.

1-Aryl-3-[4'-(p-methylbenzyloxy)-3'-methoxyphenyl]-propenones

Yield 76%, m.p. 112^{0}C; IR(KBr): ν 2968,2841,1456 (Alkane,-CH_3), 1255 (-OCH_3), 1255 (Ar-O-C), 1663 (C=O), 1591 str. (C=C), 3064,1511,1133,806 (Aromatic), cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 3.84, (s,6H,-OCH_3), 7.00 & 7.20 (d,2H,-CH=CH-), 5.08(s,2H,-O-CH_2-), 6.96-8.05(m,11H, ArH),.Mass m/z 388.M.F.:$C_{25}H_{24}O_4$.

General procedure for the preparation of 3-Aryl-5-[4'-(p-methylbenzyloxy)-3'-methoxyphenyl]-4,-5-dihydro-1H-pyrazoles (1a-l)

A mixture of Hydrazine hydrate (0.05M), 1-Aryl-3-[4'-(p-methylbenzyloxy)-3'-methoxyphenyl]-prop-2-en-1-one (1a-l) (0.05M) and NaOH (0.01M) in methanol was refluxed with stirring about (8-10hrs) untiill complete the reaction which was monitored by formation of precipitation of pyrazoline products.

3-Aryl-5-[4'-(p-methylbenzyloxy)-3'-methoxyphenyl]-4,-5-dihydro-1H-pyrazoles (1a-l)

Yield 72%, m.p. 155^{0}C; IR(KBr): ν 2939,1460 (Alkane,-CH_3), 1257 (-OCH_3), 1228 (Ar-O-C), 1595 (C=N), 3014,1506,1139 (Aromatic), 2310 (-NH-), cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 2.37, 2.33 (s,6H,-CH_3), 13.7 (dd,1H,-CH-,pyr), 5.11 (s,2H,-O-CH_2-), 6.77-7.82 (m,12H, ArH), 3.80 (s,3H,-OCH_3) .Mass m/z 385. M.F.$C_{25}H_{26}N_2O_2$.

General procedure for the preparation of 3-Aryl-1-Carbothioamide-5-[4'-(p-methylbenzyloxy)-3'-methoxyphenyl]-4,-5-dihydro-1H-pyrazoles (2a-l)

A mixture of 1-(p-Methoxyphenyl)-3-[4'-(p-methylbenzyloxy)-3'-methoxyphenyl]-prop-2-en-1-one (4.08g,0.01M) in methanol (20ml) and thiosemicarbazide (0.92g,0.01mol) and KOH(0.025M) was refluxed for 7-8hrs.The product was isolated and crystallized from ethanol. (2a-l).

3-Aryl-1-Carbothioamide-5-[4'-(p-methylbenzyloxy)-3'-methoxyphenyl]-4,-5-dihydro-1H-pyrazoles (2a-l)

Yield 73%, m.p. 122^{0}C; IR(KBr) : ν 2936,1459 (Alkane,-CH_3), 1253 (-OCH_3), 1229 (Ar-O-C), 1652 (C=N), 3009,1512,1133 (Aromatic), 3234 (-NH-), cm^{-1}; ^{1}H-NMR ($CDCl_3$) : δ 3.89, 3.95 (s,6H,- oCH_3) , 1.55 (s,2H,-NH_2), 5.17 (s, 2H, -O-CH_2-) ,6.87-8.04 (m,14H, Ar-H), 2.35 (s,3H,-CH_3) .Mass m/z 462 . M.F.:$C_{26}H_{27}N_3O_3S$.

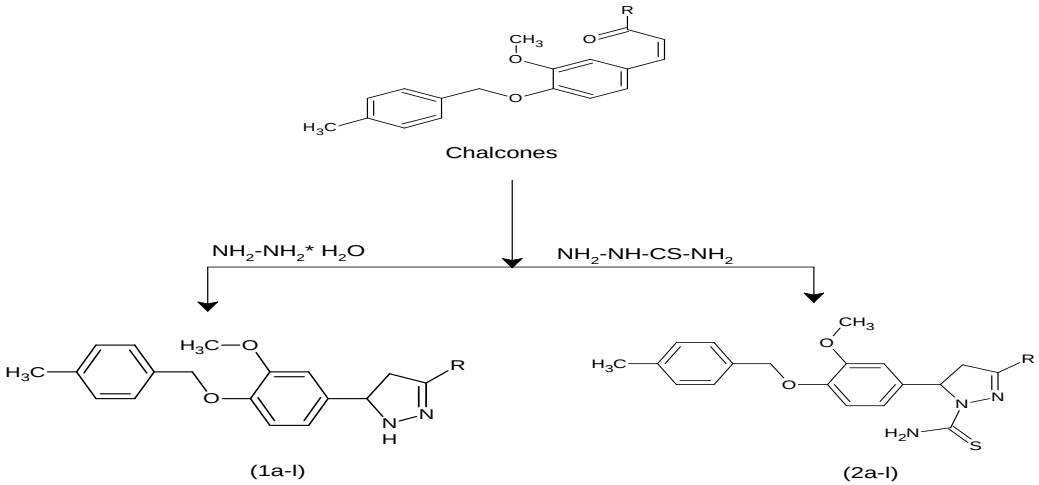
Table 1: Characterization data of the compounds (1a-l) and (2a-l).

Compd no.	R	Molecular formula	Mole.Wt.	M.P. (^{0}C)	Nitrogen %	
					Found	Calcd
1a	-C_6H_5	$C_{24}H_{24}N_2O_2$	372.5	102	7.51	7.21
1b	-4-NH_2-C_6H_4	$C_{24}H_{25}N_3O_2$	387.5	95	10.83	10.65
1c	-4-Br-C_6H_4	$C_{24}H_{23}BrN_2O_2$	451.5	68	6.20	6.11
1d	-4-Cl-C_6H_4	$C_{24}H_{23}ClN_2O_2$	407	170	6.87	6.70
1e	-2,4-(Cl_2)- C_6H_3	$C_{24}H_{22}Cl_2N_2O_2$	441	>200	6.34	6.29
1f	-2-OH- C_6H_4	$C_{24}H_{24}N_2O_3$	388.5	110	7.20	7.11
1g	-3-OH- C_6H_4	$C_{24}H_{24}N_2O_3$	388.5	92	7.20	7.03
1h	-4-OH- C_6H_4	$C_{24}H_{24}N_2O_3$	388.5	98	7.20	7.11
1i	-4-OCH_3- C_6H_4	$C_{25}H_{26}N_2O_3$	402.5	230	6.95	6.91
1j	-4-CH_3- C_6H_4	$C_{25}H_{26}N_2O_2$	386.5	155	7.24	7.21
1k	-3-NO_2- C_6H_4	$C_{24}H_{23}N_3O_4$	417.65	65	10.05	10.01
1l	-4-NO_2- C_6H_4	$C_{24}H_{23}N_3O_4$	417.65	72	10.05	10.02
2a	-C_6H_5	$C_{25}H_{25}N_3O_2S$	431.5	122	9.70	9.24
2b	-4-NH_2-C_6H_4	$C_{25}H_{26}N_4O_2S$	446.5	110	12.50	12.34
2c	-4-Br-C_6H_4	$C_{25}H_{24}BrN_3O_2S$	510.5	90	8.22	8.02
2d	-4-Cl-C_6H_4	$C_{25}H_{24}ClN_3O_2S$	466	106	9.01	8.98
2e	-2,4-(Cl_2)- C_6H_3	$C_{25}H_{23}Cl_2N_3O_2S$	500.5	100	8.40	8.32
2f	-2-OH- C_6H_4	$C_{25}H_{25}N_3O_3S$	447.5	82	9.38	9.30
2g	-3-OH- C_6H_4	$C_{25}H_{25}N_3O_3S$	447.5	112	9.38	9.29
2h	-4-OH- C_6H_4	$C_{25}H_{25}N_3O_3S$	447.5	75	9.38	9.28
2i	-4-OCH_3- C_6H_4	$C_{26}H_{27}N_3O_3S$	461.5	122	9.10	9.01
2j	-4-CH_3- C_6H_4	$C_{26}H_{27}N_3O_2S$	445.5	120	9.40	9.31
2k	-3-NO_2- C_6H_4	$C_{25}H_{24}N_4O_4S$	476.5	81	11.75	11.67
2l	-4-NO_2- C_6H_4	$C_{25}H_{24}N_4O_4S$	476.5	142	11.75	11.68

Table 2:

Compd no.	Antibacterial activity (zone of inhibition in mm)				Antifungal activity
	S.aureus	B.subtillis	E.coli	P.vulgaris	A.niger
1a	12	16	17	16	17
1b	19	15	16	20	15
1c	22	17	18	18	16
1d	17	17	19	15	15
1e	19	13	17	17	23
1f	0	14	16	16	18
1g	17	17	19	17	19
1h	19	20	21	19	20
1i	21	19	23	23	22
1j	20	21	17	20	18
1k	18	22	19	17	16
1l	17	21	22	14	20
2a	11	16	16	13	14
2b	17	15	17	14	15
2c	21	19	16	17	16
2d	15	14	20	15	18
2e	10	16	21	12	22

2f	18	17	16	18	16
2g	20	19	14	18	18
2h	22	20	18	19	20
2i	15	14	22	21	21
2j	16	23	20	17	17
2k	18	17	16	20	19
2l	19	22	19	14	23
Ampicillin	22	20	21	24	0
Amoxicillin	20	23	22	21	0
Norfloxacin	19	20	23	22	0
Benzyl penicillin	21	21	19	18	0
Griseofulvin	0	0	0	0	25



Scheme 1.

CONCLUSION

The present study leads to a convenient synthetic method for the synthesis of new compounds. Which show significant antibacterial and antifungal activity. Further investigation with appropriate structural modification of the above compounds may result in therapeutically useful products.

ACKNOWLEDGMENT

The authors are thankful to authorities of Kamani Science College, Amreli for providing research facilities and we are also thankful to Department of Chemistry Saurashtra University Rajkot for I.R., N.M.R., Mass spectral & elemental analysis.

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