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Synthesis, Characterization and Antimicrobial activities of some new Pyrazole-1-carbothioamide derivatives.

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Abstract: ***Some new 5-Aryl-3-[4'-(o-chlorobenzyloxy)-3'-methoxy-phenyl]-1-carbothioamide-4, 5-dihydro-1H-pyrazole derivatives 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: Chalcones & Pyrazoline derivatives, Antimicrobial activities.

I. INTRODUCTION

Pyrazoline derivatives are induce with different therapeutic activities such as antimicrobial, analgesic, anthelmintic, anti-inflammatory, antitubercular, etc. These valid observations led us to synthesize some pyrazoline derivatives bearing chlorobenzyloxy derivative of some chalcones. The chemistry of chalcones[1-3] containing an active keto-ethylenic linkage has been assumed important because of their versatility in the synthesis of many heterocyclic compounds. The presence of reactive α, β-unsaturated keto function in chalcones is found to be responsible for their antiallergic[4] and anticonvulsant[5-6]. Chalcones constitute an important group of natural products and some of them possess wide range of biological activity such as bactericidal[7-8], antidiabetic[9], analgesic[10-11], tranquilizer[12]etc. Pyrazoline derivative[13-16] have been found to possess wide range of therapeutic activity such as diuretic[17], fungicidal[18], herbicidal[19] and insecticidal[20] etc.

Therapeutically importance of Pyrazoline is used considerable interest to synthesize Pyrazoline of type-(2a-l) by the cyclocondensation of 1-(p-Methoxyphenyl)-3-[4'-(o-chlorobenzyloxy)-3'-methoxy-phenyl]-propenones of type-(1a-l) with thiosemicarbazide in order to study their biodynamic behavior.

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 [21] by measuring the zone of inhibition in mm. All the compounds were screened *in vitro* for their antimicrobial activities[22] against varieties of bacterial strains such Staphylococcus aureus, *Bacillus subtillis*, *Escherichia coli*, Proteus vulgaris and fungi *Aspergillus niger* at 40 µg concentration. Standard drugs like Ampicillin, Amoxicillin, Norfloxacin, Benzyl penicillin and Griseofulvin were used for comparison purpose (Table-2).

II. 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-Schmidt condensation in presence base catalyst to give chalcone derivatives (1a-l), which in next step were refluxed with thiosemicarbazide 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.

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A. Antibacterial Activity

The screening data indicated that among Carbothioamide derivatives, tested compounds **2c, 2i, 2j** and 2**k** showed good activity against *S. aureus.* However, the compounds **2f, 2h, 2i** and 2**k** showed substantial activity against *B.subtilis.* The compounds **2a, 2f, 2h** and **2k** which possesses very good against *E.coli.* However, the compounds **2a, 2e, 2f** and 2**g** showed greater degree of antibacterial activity against *P.vulgaris.* All the compounds were found to possess moderate to good activity against Gram positive and Gram negative strains.

B. Antifungal Activity

The screening data indicated that among Carbothioamide derivatives, tested compounds **2d, 2h, 2i** and **2l** exhibited good to excellent activity against *A.niger.* All other compounds exhibit mild to moderate antifungal activity against *A.niger.*

The antibacterial activity was compared with standard drug viz. Ampicillin, Amoxicillin, Norfloxacin, Penicillin and antifungal activity was compared with standard drug viz. Griseofulvin.

III. 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.

A. General procedure for the preparation of 1-Aryl-3-[4'-(o-chlorobenzyloxy)-3'-methoxyphenyl]-propenones (1a-l)

Take a mixture of 4-[(2-chlorobenzyl)oxy]-3-methoxy benzaldehyde (1) (0.01M) and 4-methoxy acetophenone (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 neutralized with dil.HCl and ethanol is added for crystallization.

B. 1-Aryl-3-[4'-(o-chlorobenzyloxy)-3'-methoxyphenyl]-propenones (1a-l)

Yield 72%, m.p. 70^0C; IR(KBr) : ν 2951,2874,1466 (Alkane,-CH_3), 1260 (-OCH_3) ,640 (-C-Cl); 1235 (Ar-O-C) , 1672 (C=O) , 1583 (C=C) ,3061,1506,1163,818 (Aromatic) ,cm^{-1}; ^{1}H-NMR ($CDCl_3$) : δ 3.88, (s,6H,-OCH_3) , 6.86 & 7.73 (d,2H,-CH=CH-), 5.15(s,2H,-O-CH_2-) ,6.96-8.03(m,11H, ArH) , .Mass m/z 408.5 .M.F.:$C_{24}H_{21}O_4Cl$.

C. General procedure for the preparation of 3-Aryl-5-[4'-(o-chlorobenzyloxy)-3'-methoxyphenyl]-4,-5-dihydro-1H-pyrazoles (2a-l)

A mixture of 1-(p-methoxyphenyl)-3-[4'-(o-chlorobenzyloxy)-3'-methoxy-phenyl]-propenone (4.08g, 0.01M) in methanol (20ml) and thiosemicarbazide (0.92 g, 0.01mol) & KOH (0.025 M), was refluxed for 7-8 hrs. The product was isolated and crystallized from ethanol.

D. 3-Aryl-5-[4'-(o-chlorobenzyloxy)-3'-methoxyphenyl]-4,-5-dihydro-1H-pyrazoles(2a-l)

Yield 77%, m. p. 135^o C; IR(KBr) : ν 2941.26, 1452.51 (Alkane,-CH_3), 1239.59 (-OCH_3) ,747.88 (-C-Cl); 1213.82 (Ar-O-C) , 1679.94 (C=N) , 3002.44,1503.54,1136.81,834.42 (Aromatic), 3396.64 (-NH), 1597.77 (C=S) cm^{-1}; ^{1}H-NMR ($CDCl_3$) : δ 5.30 (s,2H,-O-CH_2-) ,6.86-8.06 (m,14H, ArH), 3.89 & 3.98 (s,6H,-OCH_3), 8.01 (s,2H,-CS-NH_2) .Mass m/z 481.5 . M.F.: C_{25} $H_{24}ClN_3O_3S$.

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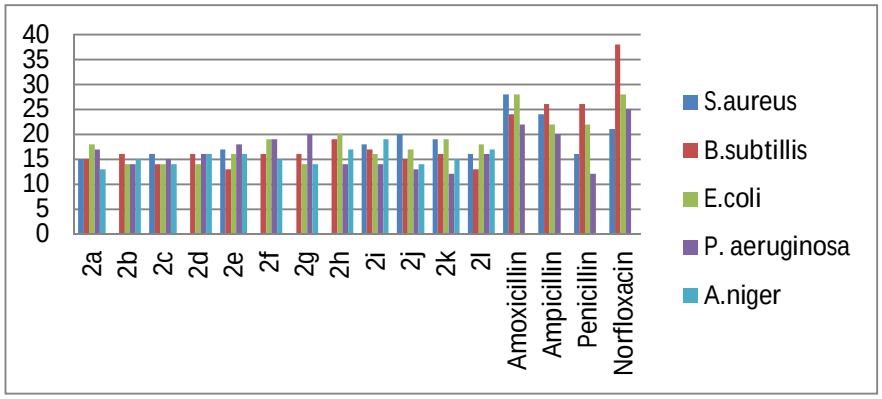
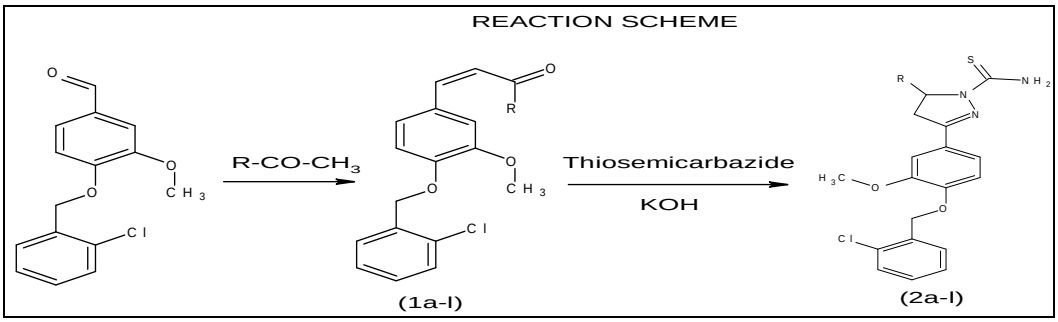
Table-1

compd. no.	R	Molecular formula	Molecular weight	M.P. ^{0}C	% yield	% of N calc.	found.
2a	-C_6H_5	$C_{24}H_{22}ClN_3O_2S$	451.5	118	66	9.30	9.24
2b	-4-NH_2-C_6H_4	$C_{24}H_{23}ClN_4O_2S$	466,5	123	65	12.00	11.84
2c	-4-Br-C_6H_4	$C_{24}H_{21}BrClN_3O_2S$	530.5	137	70	7.92	7.90
2d	-4-Cl-C_6H_4	$C_{24}H_{21}Cl_2N_3O_2S$	486	126	68	8.64	8.61
2e	-2,4-(Cl_2)-C_6H_3	$C_{24}H_{20}Cl_3N_3O_2S$	520.5	109	71	8.07	8.01
2f	-2-OH- C_6H_4	$C_{24}H_{22}ClN_3O_3S$	467.5	86	75	8.98	8.93
2g	-3-OH- C_6H_4	$C_{24}H_{22}ClN_3O_3S$	467.5	90	60	8.98	8.92
2h	-4-OH- C_6H_4	$C_{24}H_{22}ClN_3O_3S$	467.5	101	68	8.98	8.93
2i	-4-OCH_3- C_6H_4	$C_{25}H_{24}ClN_3O_3S$	481.5	135	77	8.72	8.70
2j	-4-CH_3- C_6H_4	$C_{25}H_{24}ClN_3O_2S$	465.5	124	66	9.02	9.00
2k	-3-NO_2- C_6H_4	$C_{24}H_{21}ClN_4O_4S$	496.5	101	64	11.28	11.22
2l	-4-NO_2- C_6H_4	$C_{24}H_{21}ClN_4O_4S$	496.5	158	69	11.28	11.25

Table-2



Scheme-1



IV. 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.

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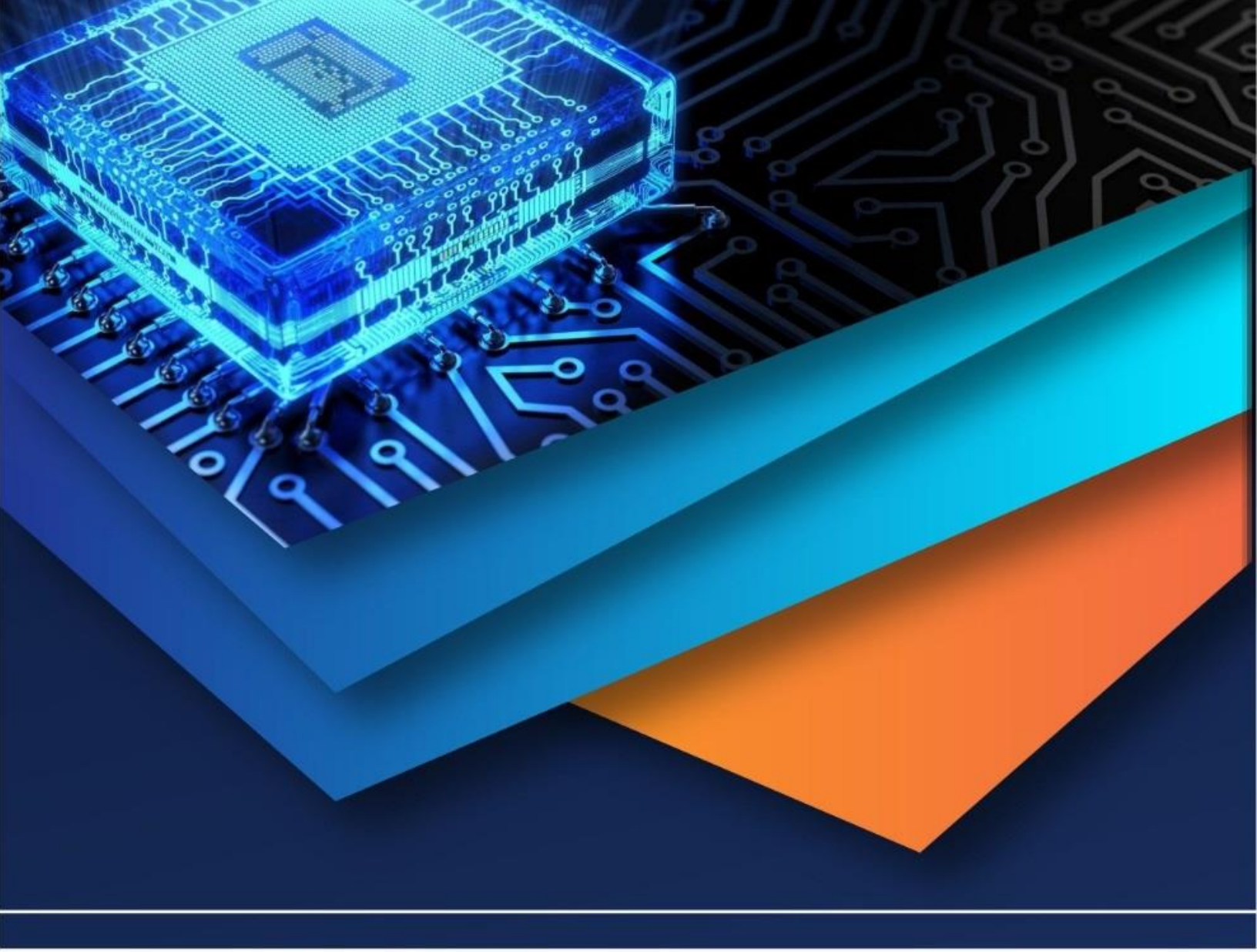

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