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Synthesis and Biological Evaluation of N-(4-(5-Aryl-4, 5-Dihydro-1H-Pyrazol-3-yl) Phenyl) Cyclopropane Carboxamide

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Abstract*: Different pyrazoline derivatives were synthesized by cyclization of substituted chalcones with Hydrazine hydrate. Some new N-(4-(3-Aryl-acryloyl)phenyl)cyclopropane carboxamide (1a-l) and N-(4-(5-Aryl-4,5-dihydro-1H-pyrazol-3-yl)phenyl)cyclopropane carboxamide (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: Chalcones, Pyrazoline, Antimicrobial activities.

I. INTRODUCTION

The chemistry of chalcones containing an active keto-ethylenic linkage has been assumed important because of their versatility in the synthesis of many heterocyclic compounds. Pyrazoline derivatives have been found to contain wide range of therapeutic activity such as antidiabetic[7] ,antiimplantation[8] , antiallergic[9] , anticonvulsant[10-11] ,antineoplastic[12], antiinflammatory[13], antitumor[14], analgesic[15-16] antimicrobial[17], bactericidal[18-20] etc. Pyrazolines 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 N-(4-(5-Aryl-4,5-dihydro-1H-pyrazol-3-yl)phenyl)cyclopropane carboxamide (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 synthesized compounds have been evaluated for their antibacterial activity towards Gram positive bacterial strains such as B.subtilis and S.aureus whereas E.coli and P.aeruginosa were Gram negative bacterial strains and antifungal activity towards A.niger at a concentration of 40 µg and synthesized compounds has been compared with standard drugs. Standard drugs like Ampicillin, Chloramphenicol, Norfloxacin, and Griseofulvin were used for comparison purpose. (Table-1)

II. 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 (400MHz) using TMS as an internal standard, chemical shift in δ ppm.

A. General Procedure for the Preparation of n-(4-(3-(4-Methoxyphenyl)Acryloyl)phenyl) Cyclopropane Carboxamide (1a-l)

A mixture of N-(4-acetylphenyl)cyclopropane carboxamide 0.5 gm(0.01 mol) with 4-methoxy benzaldehydes 0.33 gm/0.29 ml (0.01 mol) using Claisen-Schmidt condensation method in presence of 40% NaOH using methanol as a solvent at room temperature under

stirring for 8 hours. Reaction was monitored by TLC. Reaction mass was poured into chilled water. Product was filtered and dried. It was recrystallized from ethanol. Yield 81.25%, M.P.162-164^{0}C, Elemental Analysis Calculated for $C_{20}H_{19}NO_3$ Requires: C-74.75%; H-5.96%, N-4.36%; O-14.94%, Found: C-74.70%; H-5.93; N-4.31%; O-14.91%,

B. N-(4-(3-(4-Methoxyphenyl)Acryloyl)phenyl)Cyclopropane Carboxamide (1a-l)

Yield 81.25%, M.P.162-164^{0}C; IR(KBr) : ν Alkane C-H str. (asym.) 2938, C-H def.(asym.) 1417, , C-H o.o.p.(def) 1352, Aromatic C-H str. 3040 ,C=C str.1598,1511, Amine C-N str. 1294 ,N-H str. 3241, Ether C-O-C str. 1256, Ketone C=O str. 1658, Vinyl CH=CH str. 3040, cm-1; 1H-NMR ($CDCl_3$) : δ 0.80-1.51, (m,5H, Cyclopropane) ,3.748 (s, 3H,-OCH_3), 7.19 & 7.37 (d-d, 2H, CH=CH) , 6.85-7.86 (m,8H, Ar-H), 10.48 (s, 1H, 2^{0}Amide), Mass m/z 322.5 (M^+); .M.F.: $C_{20}H_{19}NO_3$

C. General Procedure for the Preparation of N-(4-(5-(4-Methoxyphenyl)-4,5-Dihydro-1H-Pyrazol-3-yl)Phenyl)Cyclopropane Carboxamide (2a-l)

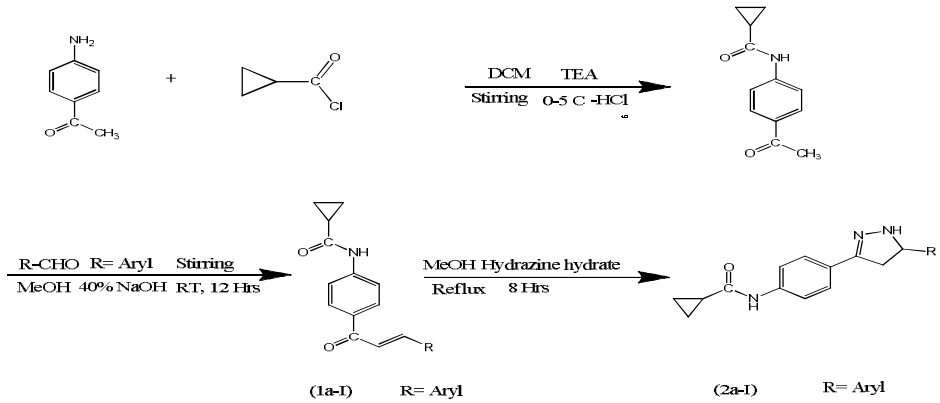
A mixture of N-(4-(3-(4-methoxyphenyl)acryloyl)phenyl)cyclopropane carboxamide 0.5 gm(0.01 mol) with hydrazine hydrate 0.23 gm/0.22 ml (0.03 mol) in methanol was refluxed about 8 hours until complete the reaction which was monitored by TLC. The reaction mass was poured into chilled water and product was filtered and dried. It was recrystallized from ethanol. Yield 81.73%, M.P.210-212^{0}C, Elemental Analysis Calculated for $C_{20}H_{21}N_3O_2$ Requires:C-71.62%;H-6.31%;N-12.53%;
O-9.54%, Found: C-71.58%; H-6.28%; N-12.50%; O-9.49%,

D. N-(4-(5-(4-Methoxyphenyl)-4,5-Dihydro-1H-Pyrazol-3-yl)phenyl)Cyclopropane Carboxamide (2a-l)

Yield 81.73%, M.P.210-212^{0}C IR(KBr) : Alkane C-H str. (asym.) 2942, Aromatic C=C str. 1595, 1511, C-H o.o.p.(def) 821, Ether C-O-C str. 1246, Pyrazoline C=N str. 1595, N-H str.3328 cm$^{-1,}$

^{1}H-NMR (DMSO) : δ 0.80-1.79, (m,5H, Cyclopropane), 3.73 (s, 3H,-OCH_3), 4.75 (t,1 H, Pyrazoline ring), 7.4, (s, 1H,Pyrazoline – NH), 2.77, 3.39 (d, 2H,Pyrazoline ring), 10.28 (s, 1H, 2^{0}Amide), 6.88-7.62 (m,8 H, Ar-H). .Mass m/z 336.5 (M+) . M.F.$C_{20}H_{21}N_3O_2$

III. REACTION SCHEME



IV. 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.

V. 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. Ampicillin, Chloramphenicol, Norfloxacin and antifungal activity was compared with standard drug viz. Griseofulvin.

TABLE-1

Characterization data of the compounds (2a-l) :						
Compound No.	R	Molecular Formula	Molecular Weight	M.P. (^{0}C)	Nitrogen %	
					Found	Calcd
2a	-C_6H_5	$C_{19}H_{19}N_3O_3$	305.37	166-170	13.71	13.76
2b	-4-OCH_3-C_6H_4	$C_{20}H_{21}N_3O_2$	335.40	210-212	12.50	12.53
2c	-4-$N(CH_3)_2C_6H_4$	$C_{21}H_{24}N_4O$	348.44	212-215	16.03	16.08
2d	-C_4H_3O	$C_{17}H_{17}N_3O_2$	295.34	208-210	14.20	14.23
2e	-2-Cl-C_6H_4	$C_{19}H_{18}ClN_3O$	339.82	208-210	12.32	12.37
2f	-4-F-C_6H_4	$C_{19}H_{18}FN_3O$	323.36	90-92	12.95	12.99
2g	-4-OH-C_6H_4	$C_{19}H_{19}N_3O_2$	321.37	178-181	13.06	13.08
2h	-4-OH-3-OCH_3-C_6H_3	$C_{20}H_{21}N_3O_3$	351.40	192-194	11.95	11.96
2i	-2-OH-C_6H_4	$C_{19}H_{19}N_3O_2$	321.37	175-177	13.05	13.08
2j	-2-NO_2-C_6H_4	$C_{19}H_{18}N_4O_3$	350.37	165-168	15.94	15.99
2k	-4-Cl-C_6H_4-	$C_{19}H_{18}ClN_3O$	339.82	203-205	12.33	12.37

TABLE-2

Antimicrobial Activity: (Zone of inhibition in mm) :					
Compound No.	E. coli	B.subtilis	P.aeruginosa	S. aureus	A . Niger
2a	16	10	12	13	08
2b	10	15	10	12	07
2c	11	16	11	10	10
2d	12	11	12	11	11
2e	10	9	10	12	09
2f	8	11	11	10	12
2g	11	12	10	11	13
2h	12	13	9	12	11
2i	15	11	11	15	10
2j	14	16	12	16	9
2k	11	18	10	13	8
Ampicillin	18	19	13	10	0
Chloramphenicol	13	15	15	12	0
Norfloxacin	15	14	12	13	0
Griseofulvin	0	0	0	0	14

VI. RESULTS AND DISCUSSION

The synthesis of N-(4-(3-Aryl-acryloyl)phenyl)cyclopropane carboxamide (1a-l) and N-(4-(5-Aryl-4,5-dihydro-1H-pyrazol-3-yl)phenyl)cyclopropane carboxamide (2a-l) was Warried ouT in two steps, first by the condensation of N-(4-acetylphenyl)cyclopropane carboxamide) with different aromatic aldehydes by Claisen-Schmidt 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) (Reaction Scheme).

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.

VII. CONCLUSION

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

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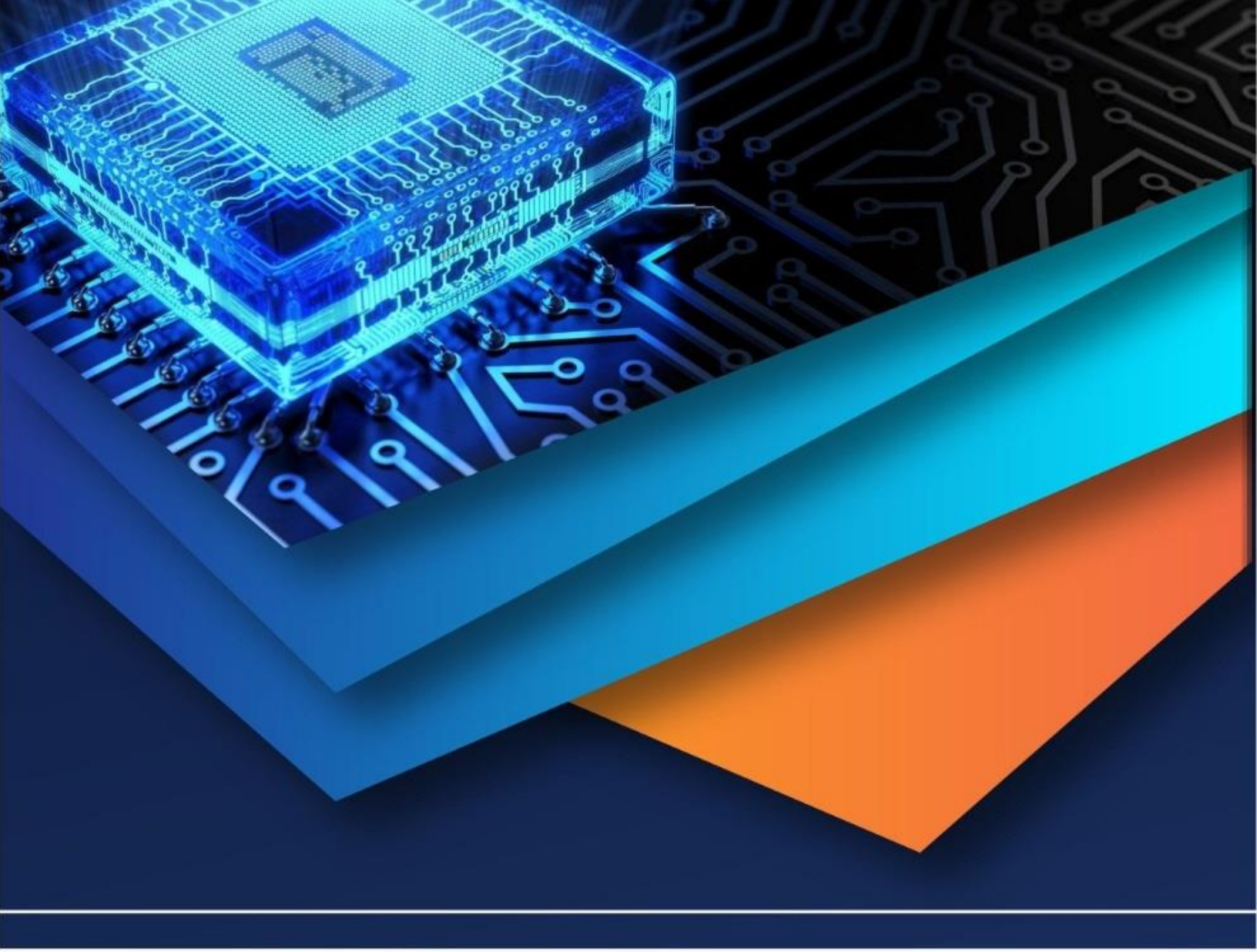

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