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Synthesis and Biological Evaluation of N-[4-(5-Aryl-2,5-Dihydroisoxazol-3-Yl)Phenyl]Cyclopropane Carboxamide

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''SYNTHESIS AND BIOLOGICAL EVALUATION OF N-[4-(5-ARYL-2,5-DIHYDROISOXAZOL-3-YL)PHENYL]CYCLOPROPANE CARBOXAMIDE''

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ABSTRACT
Isoxazoles have been reported to have various pharmacological activities like antibacterial, antifungal, insecticidal etc. In order to attain better drug potency, we have prepared isoxazole derivatives of type (II) by the condensation of N-(4-(3-Aryl-acryloyl)phenyl)cyclopropane carboxamide of type (I) with hydroxylamine hydrochloride in presence of KOH., all the synthesized compounds were characterized by TLC, ^{1}H NMR, Mass spectral data and IR. All the synthesized compounds (2a-1) were screened for their antimicrobial activity at 40 µg concentration.

Keywords: *Isoxazole, Antibacterial activity, Antifungal activity.*

1. INTRODUCTION

Isoxazole is a heterocyclic compound having five members with two hetero atoms: oxygen at position 1 and nitrogen at position 2.Claisen first reported an isoxazole (I) for a product from the reaction of 1,3 diketone with hydroxylamine in year 1888, Afterward a solid foundation for the chemistry of isoxazole was laid down by Claisen and his students. It was shown to possess typical properties of an aromatic system but under certain reaction conditions. Particularly in reducing or basic media, it becomes very highly labile.

The structure elucidation of synthesized compounds has been done on the basis of Elemental analysis, Infrared and ^{1}H Nuclear Magnetic Resonance spectroscopy and further supported by Mass spectrometry. Purity of all compounds has been checked by thin layer chromatography. All the compounds have been evaluated for their in vitro biological assay like antibacterial activity towards Gram positive and Gram negative bacterial strains and antifungal activity towards A.niger at a concentration of 40 µg. The biological activities of synthesized compounds were compared with standard drugs.

2. MATERIALS AND METHODS

Melting points were taken in open glass capillary tubes are uncorrected. IR spectra (cm^{-1}) were recorded on Shimadzu-435-IR Spectrophotometer and 1H-NMR Spectra on Bruker Spectrometer (400MHz) using TMS as an internal standard, chemical shift in δ ppm.

2.1 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 benzaldehyde 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%, 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}; ^{1}H-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, ^{1}H, 2^{0}Amide), Mass m/z 322.5 (M^+); .M.F.: $C_{20}H_{19}NO_3$

2.2 General Procedure for the Preparation of N-[4-(5-Aryl-2,5-dihydroisoxazol-3-yl)phenyl]cyclopropane carboxamide(2a-l).

A mixture of N-{4-[3-(4-Methoxyphenyl)acryloyl]phenyl}cyclopropane carboxamide 0.5 gm (0.01mol) and hydroxylamine hydrochloride 0.10 gm (0.01 mol) was dissolved in methanol using KOH as catalyst. The whole reaction mass was refluxed for 12 hrs. The reaction mixture was poured into crushed ice. Solid separated was filtered and recrystallized from ethanol. Yield 77.91%, M.P. 191^{o}C. Elemental Analysis Calculated for $C_{20}H_{20}N_2O_3$; Requires : C-71.41%; H-5.99%; N-8.33 %; O-14.27 % ; Found: C-71.36%; H-5.95; N-8.31%; O-14.24%. Similarly, other N-[4-(5-Aryl-2,5-dihydroisoxazol-3-yl)phenyl]cyclopropane carboxamide were prepared. The physical data are recorded in Table No.1.

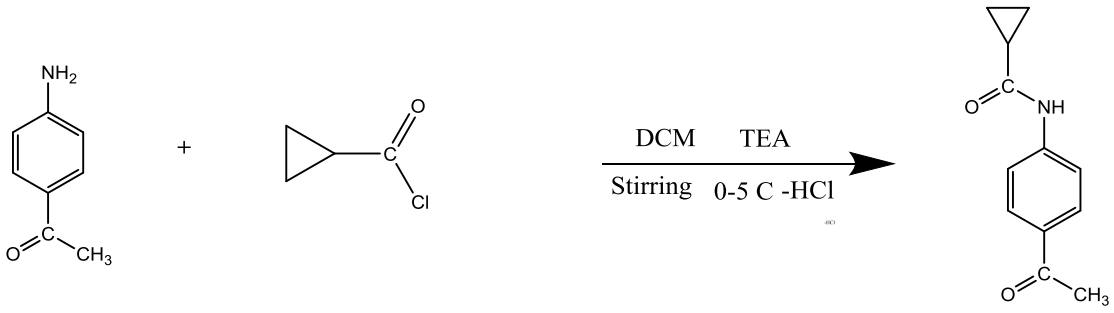
M.P. 137°C, % yield: 77.1%. Elemental analysis: Required; C, 71.04; H, 5.30; N, 6.14; C27H24N2O5; Found C, 71.01; H, 5.28; N, 6.10.

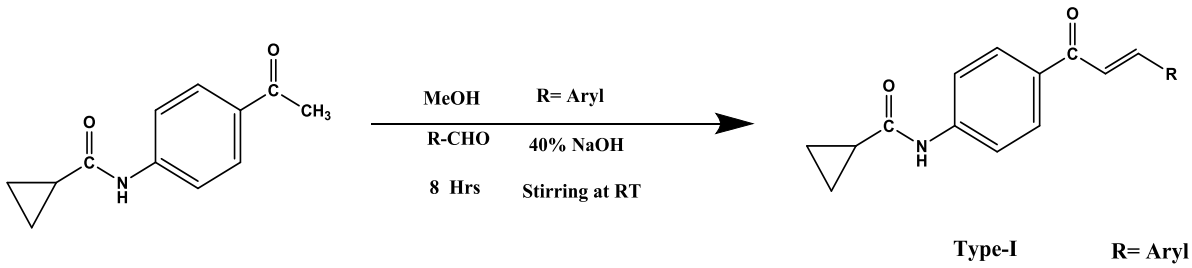
^{1}H NMR (DMSO); 3.7-3.8 (5, 4H, 2 × OCH_3); 2.0 - (5, 2H, -CH_2) – 4.8 (5, 1H, -CH); 6.9-7.8 (m, 134, Ar-H); 8.0 (5-1H-COOH)

IR (KBR) (cm^{-1}): 2920 Str. (C-H asym); 2851 C-H def (asym); 1422 (C-H 0.0.P def); 1368 (C-H Str; aromatic); 3028 (C=C Str.); 1593 (C-N Str.); 1265 (C-O-C Str.); 1705 (>C=O Str.); 3028 (Vinyl –CH=CH Str.)

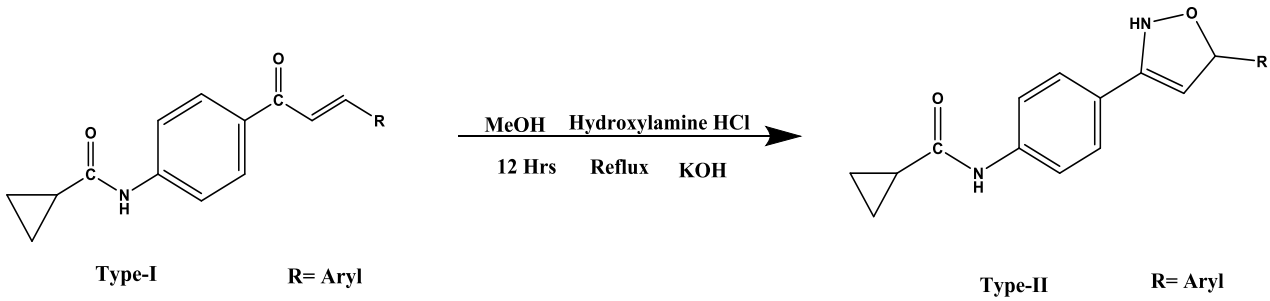
M/Z: 456, 412, 367, 354, 322, 308, 307, 293, 277, 264, 248, 231, 218, 205, 191, 177, 162, 151, 131, 117, 105 (B.P); 91, 77, 65, 44, 41.

2.3 REACTION SCHEME





(1a-1)



(2a-1)

Table 1: Physical Constants of compound (2a-1)

Sr. No.	Ar	M.F.	M.W.	M.P. (^{o}C)	% Yield	% NITROGEN	
						Th	Found
2a	-C_6H_5	$C_{19}H_{18}N_2O_2$	306.36	210	74.32	9.14	9.12
2b	-4-OCH_3-C_6H_4	$C_{20}H_{20}N_2O_3$	336.38	191	77.91	8.33	8.31
2c	-4-$N(CH_3)_2C_6H_4$	$C_{21}H_{23}N_3O_2$	349.43	147	81.32	12.03	12.00
2d	-C_4H_3O	$C_{17}H_{16}N_2O_3$	296.32	167	70.23	9.45	9.43
2e	-2-Cl-C_6H_4	$C_{19}H_{17}ClN_2O_2$	340.80	180	72.89	8.22	8.19

Sr. No.	Ar	M.F.	M.W.	M.P. (^oC)	% Yield	% NITROGEN	
						Th	Found
2f	-4-F-C_6H_4	$C_{19}H_{17}FN_2O_2$	324.35	127	75.98	8.64	8.61
2g	-4-OH-C_6H_4	$C_{19}H_{18}N_2O_3$	322.36	168	79.56	8.69	8.66
2h	-4-OH-3-OCH_3-C_6H_3	$C_{20}H_{20}N_2O_4$	352.38	190	73.56	7.95	7.93
2i	-2-OH-C_6H_4	$C_{19}H_{18}N_2O_3$	322.36	173	72.45	8.69	8.65
2j	-2-NO_2-C_6H_4	$C_{19}H_{17}N_3O_4$	351.36	203	70.56	11.96	11.94
2k	-4-Cl-C_6H_4	$C_{19}H_{17}ClN_2O_2$	340.80	176	76.49	8.22	8.21

ANTIMICROBIAL ACTIVITY

Table 2: Antimicrobial activity of compounds (2a – 1)

Antimicrobial Activity: (Zone of inhibition in mm)					
Compound No.	Antibacterial activity				Antifungal activity
	Gram +ve bacteria		Gram –ve bacteria		
	B. subtilis	*S. aureus*	*E. coli*	*Pseudomonas*	*A. Niger*
2a	12	15	13	13	9
2b	14	17	13	16	8
2c	15	12	12	12	14
2d	12	14	15	15	12
2e	12	13	17	11	16
2f	13	12	10	12	11
2g	14	12	12	11	8
2h	12	13	14	14	11
2i	12	14	16	12	13
2j	13	16	15	13	8
2k	16	12	12	11	13
Ampicillin	18	12	17	19	14
Chloramphenicol	17	13	15	17	11
Norfloxacin	16	15	16	15	15
Griseofulvin	0	0	0	0	0

RESULTS AND DISCUSSION

The synthesis of N-(4-(3-Aryl-acryloyl)phenyl)cyclopropane carboxamide (1a-l) and N-[4-(5-Aryl-2,5-dihydroisoxazol-3-yl)phenyl]cyclopropane (2a-l) was carried 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 hydroxyl amine hydrochloride in presence of KOH to yield isoxazole 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}HNMR and Mass Spectral data.

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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