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SYNTHESIS AND ANTIMICROBIAL STUDIES OF SOME NEW HALOGENATED ISOXAZOLINE DERIVATIVES

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ABSTRACT: A series of some new Isoxazoline derivatives derived from 3-(4'-dimethylamino-phenyl)-1-(2-hydroxyphenyl)-Propenone(chalcone) derivatives using hydroxylamine hydrochloride is reported. These newly synthesized compounds were screened for their antimicrobial potencies which reflect moderate to good activity against different strains of bacteria and fungi employed. The promising feature of this reaction is mild reaction condition and excellent yield with high purity of compounds synthesized. All the synthesized compounds were confirmed by IR, ^{1}HNMR and Mass.

INTRODUCTION: Compounds incorporating hetero-cyclic ring systems continue to attract considerable interest due to the wide range of biological activities they posses. Amongst them five membered heterocyclic compounds occupy a unique place in the realm of natural and synthetic organic chemistry. Five membered heterocycles like isoxazoline have found wide application as pharmaceutical and agrochemical agents. In recent years, an increasing attention has been given to the synthesis of isoxazoline derivatives as a source of new antibacterial agents. The synthesis of novel isoxazoline derivatives remain a main focus of medicinal research. Isoxazoline represents one of the active classes of compounds possessing a wide spectrum of biological activities.

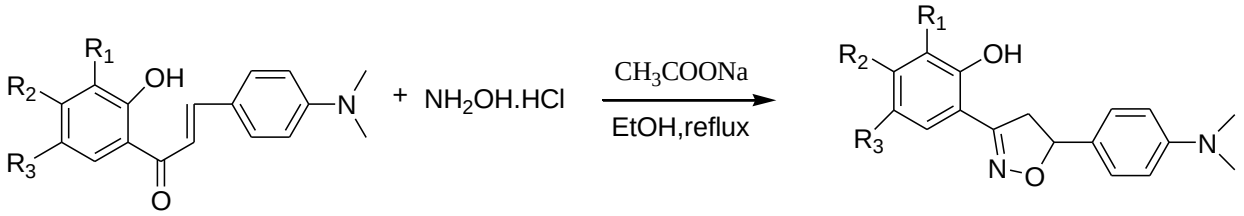
A large number of isoxazoline derivatives have been found to exhibit antifungal [1-2], antibacterial [3], anticonvulsant [4], ani-inflammatory [5], antiviral [6], analgesic [7-8], antitubercular [9-10] activities. Literature survey revealed that incorporation of halogen (chloro, bromo, iodo) moiety in isoxazoline ring and some fluorinated methyliminobenzoxazoline derivatives have been patented as plant protecting acaricids, fungicides and insecicides [11].

Much research has been carried out with the aim to find their therapeutic values. The derivatives are prepared and tested for variety of biological activities such as antidepressant [12] and hypoglycemic activity [13]. Isoxazole derivatives are used as corrosion inhibitors for fuels and lubricants [14]. Its derivatives also show a good potency in animal models of thrombosis [15]. Penicillin derivatives containing Isoxazoline ring are found to be antibacterial [16].

MATERIALS AND METHODS:

Experimental: All the melting points were determined in open capillary method and are uncorrected. IR spectra were recorded on KBr spectometer.^{1}HNMR spectra on a Bruker Avance DPX 400 MHz spectrometer with $CDCl_3$ as a solvent and TMS internal standard. The chemical shift values are expressed in part per million (ppm) downfield from the internal standard and signals are quoted as s (singlet), d (doublet), t (triplet) and m (multiplet). Purity of the compounds is checked by TLC plates (Merck) using benzene and ethyl acetate as an eluent in the ratio of (7:3 v/v).

General procedure for synthesis of Isoxazolines: A mixture of chalcone (0.01mol) and hydroxylamine hydrochloride (0.01mol) and freshly fused anhydrous sodium acetate (0.02mol) in ethanol were added and the reaction mixture was heated under reflux for 6-7 hr. After completion of reaction (monitored by TLC) the content of the flaks was poured into crushed ice. The separated solid was filtered, washed with water and dried; further purification was done by recrystallization from ethanol. The physical data of synthesized compounds are presented in **Table 1**.



2(a-j) 3(a-j)

SCHEME 1

TABLE 1: PHYSICAL DATA OF SYNTHESIZED ISOXAZOLINE DERIVATIVES (3a-j)

Sr.No.	Entry	R_1	R_2	R_3	Molecular formula	Yield (%)	M.P. ^{0}C
1	3a	Cl	H	Cl	$C_{17}H_{16}O_2Cl_2N_2$	90	135
2	3b	I	H	Cl	$C_{17}H_{16}O_2ClIN_2$	92	130
3	3c	Br	H	Cl	$C_{17}H_{16}O_2BrClN_2$	88	142
4	3d	Br	H	Br	$C_{17}H_{16}O_2Br_2N_2$	85	122
5	3e	H	H	Br	$C_{17}H_{17}O_2BrN_2$	90	140
6	3f	H	CH_3	Cl	$C_{18}H_{19}O_2ClN_2$	88	128
7	3g	Br	CH_3	Cl	$C_{18}H_{18}O_2BrClN_2$	86	136
8	3h	I	CH_3	Cl	$C_{18}H_{18}O_2ICIN_2$	85	132
9	3i	Br	H	CH_3	$C_{18}H_{19}O_2BrN_2$	87	145
10	3j	I	H	Br	$C_{17}H_{16}O_2BrIN_2$	92	150

Antimicrobial activity: Antimicrobial screening of synthesized isoxazoline compounds **(3a-j)** was conducted by using Cup Plate Method[17] at a concentration of 100µg/ml. The bioactivity of these molecules is assessed against different strains of bacteria and fungi as mentioned in Table 2. DMSO was used as solvent control. The results of antimicrobial data are summarized in Table 2. All compounds show the moderate to good activity against bacteria and fungi used.

RESULTS AND DISCUSSION: The structures of the all synthesized compounds **3(a-j)** were elucidated on the basis of, IR, ^{1}H-NMR and mass spectroscopy. Presence of aromatic ring was confirmed by absorption band around 3209 cm-^{1}. IR data of all final synthesized compounds confirms the presence of specific functional groups present in the synthesized compounds. The mass and ^{1}HNMR spectra of compounds were in conformity with assigned structures.

As indicated in **Table 2**, the antimicrobial activity of synthesized compounds is compared to standard drugs, all the synthesized compounds possessed anti-bacterial activity against all the five strains. Compounds **3b, 3c** and **3e** showed moderate activity against *Staphylococcus aureus*, *Bacillus subtilis*, *Aspergillus niger* and *Penicillium chrysogenum* as compared to standard drug. Compound **3f, 3i and 3j** exhibited good activity against *Salmonella typhi, Staphylococcus aureus* and *Bacillus subtilis.*

Spectral data of selected compounds:

3-(3-bromo-5-chloro-2-hydroxy-phenyl)-5-(4'-dimehyl amino-phenyl)-4, 5-dihydro-2-isoxazoline (2c): IR (KBr); 3209 [Ar-C-OH], 2920 [aliphatic C-H] 1612, 1519[C=N], 1098 [C-O-C], 817 cm^{-1} [N-O];^{1}H NMR; δ 2.85-3.01 (s, 6H,-N(CH_3)$_2$), δ 3.41(dd,1H,CH_A), δ 3.75 (dd, 1H, CH_B), δ 5.69 (t,1H, CH_X), δ 10.6 (s,1H,OH) δ 6.70-7.89 (m, 5H, Ar-H) ppm, Mass (m/z); 394 (m^+ ion).

3-(3, 5-dibromo-2-hydroxy-phenyl)-5-(4'-dimethyl amino-phenyl)-4, 5-dihydro-2-isoxazoline (2d): IR (KBr); 3217[Ar-C-OH], 2924 [aliphatic C-H], 1612, 1527 [C=N], 1411 [C=C], 1080[C-O-C], 825 cm^{-1} [N-O]^{1}H NMR; δ 3.42 (dd, 1H, CH_A), δ 3.72(dd, 1H, CH_B), δ 5.70 (t, 1H, CH_X) δ 2.89-3.09 (s ,6H, $(CH_3)_2$), δ 6.72-7.99 (m, 5H , Ar-H) δ 10.70 (s, 1H, OH,) ppm Mass (m/z); 440 (m^+ ion).

3-(5-Bromo-2-hydroxy-phenyl)-5-(4'-dimethylamino-phenyl)-4, 5-dihydro-2-isoxazoline (2e): IR (KBr); 3227 [Ar-C-OH], 2921 [Aliphatic C-H], 1608, 1512 [C=N], 1415 {C=C], 1081 [C-O-C], 817 cm^{-1} [N-O]^{1}H NMR; δ 3.35 (dd, 1H, CH_A), δ 3.65 (dd, 1H, CH_B), δ 5.72 (t, 1H, CH_X), δ 3.1 (s, 6H, $(CH_3)_2$), δ 6.70-8.20 (m, 6H, Ar-H), δ 10.75 (s, 1H, OH) ppm Mass (m/z); 361 (m+ ion).

TABLE 2: ANTIMICROBIAL ACTIVITY OF SYNTHESIZED ISOXAZOLINE DERIVATIVES (3a-j)

Products	Bacteria (Zone of Inhibition in mm)				Fungi (Zone of Inhibition in mm)			
	A	B	C	D	E	F	G	H
3a	--	12	21	14	-ve	-ve	-ve	-ve
3b	--	14	20	17	-ve	-ve	-ve	-ve
3c	--	12	24	17	-ve	-ve	-ve	-ve
3d	--	13	21	16	-ve	-ve	-ve	-ve
3e	--	14	24	14	-ve	-ve	-ve	-ve
3f	--	12	22	17	-ve	-ve	-ve	-ve
3g	--	15	21	15	-ve	-ve	-ve	-ve
3h	--	14	24	15	-ve	-ve	-ve	-ve
3i	--	16	22	16	-ve	-ve	-ve	-ve
3j	--	13	21	18	-ve	-ve	-ve	-ve

A= *Escherichia coli, B=Salmonella typhi, C= Staphylococcus aureus, D=Bacillus subtilis; E= Aspergillus niger, F=penicillium chrysogenum, G=Fusarium moneliforme, H= Aspergillus flavus.* -- = No Antibacterial activity, -ve = Growth (Antifungal Activity Observed)

CONCLUSION: In conclusion, we have synthesized some new isoxazolines derivatives. The newly synthesized isoxazolines are characterized by spectral data and further evaluated for antimicrobial activity. The results obtained clearly indicate that the synthesized compounds possess significant antibacterial as well as antifungal activity.

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