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Synthesis of Bioactive Isothiazoline Derivatives

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In present, some nitrogen and sulfur containing heterocycles are synthesized. The compounds 3-(2'-hydroxy-3'-iodo-4'-ethoxy-5-bromo phen-l'-yl)-5-substituted-2- isoxazoline have been synthesized by the condensation of 2'-hydroxy-3'-iodo-4'-ethoxy-5-bromo substituted chalcone with hydroxylamine hydrochloride to produce isoxazoline, which again treated with P_2S_5 in presence of pyridine to give 3-(2'-hydroxy-3'-iodo-4'-ethoxy-5'-bromo phen-l'-yl)-5-substituted-2- isothiazoline. All the compounds have been characterized by elemental analysis IR, NMR and Mass spectral data. All the compounds have been screened for their antimicrobial activity to gram positive and gram negative bacterial strains and antifungal activity.

Key Words: Synthesis, Isothiazoline derivatives.

INTRODUCTION

Isoxazolines and their derivatives are one of the known heterocyclic compounds, which contain nitrogen and oxygen as heteroatoms and are important chemotherapeutic agents. The survey of literature indicates that there are three type of isoxazolines, 2-isoxazoline, 3-isoxazoline and 4-isoxazoline. Initially, the 3,5-diphenyl-2-isoxazoline was isolated from the reaction of *p*-chloro-phenyl propiophenone with hydroxylamine[1].

Large number of isoxazoline derivatives have been found to possess antibacterial[2-4], antituberculer[5], antidiabeties[6] and antifungal activity[7,8].

EXPERIMENTAL

Melting points were taken in open capillaries and are uncorrected. The IR spectra were recorded on a Shimadzu FTIR 8400 spectrophotometer, PMR spectra were recorded on a Bruker (300 MHz) spectrometer using TMS as internal standard and Mass spectra were recorded on a Jeol SX-l 02 (F AB) Mass spectrometer.

General procedure for the preparation of 3-(2'-hydroxy-3'-iodo-4'-ethoxy-5'-bromo phen-l'-yl)-5-substituted phenyl-2-isoxazoline [la-i]: A mixture of 2'-hydroxy-3'-iodo-4'-ethoxy-5'-bromo substituted phenyl chalcone (0.01 mol), hydroxylamine hydrochloride (0.02 mol) and aq. KOH (2 mL) was refluxed in ethanol (30 mL) for 4 to 5 h. The reaction mixture was cooled and acidified by 1:1 HCl in ice cold condition. Separated solid was filtered and crystallized from ethanol as yellowish needles. The physical data of the synthesized compounds are given in Table-1.

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lc: IR (KBr, ν_{max}, cm^{-1}) : 3390 (Ar-OH), 2864 (C- H), 1622 (C=N), 1060 (C-N), 608 (C-Br), 545 (C-I). **Id:** NMR (δ ppm): 1.46-1.58 (t, 3H), 4.15-4.2 (q, 2H), 3.01-3.18 (dd, 1H), 3.57-3.68 (dd, 1H), 5.43 (dd, 1H), 5.88 (s, 1H) 7.12-7.36 (m, 5H). **la:** Mass (m/z): 489 (m + 1).

General procedure for the preparation of 3-(2'-hydroxy-3'-iodo-4'-ethoxy-5'-bromo phen-l'-yl)-5-substituted phenyl-2-isothiazoline [2a-i]: A mixture of 3-(2'-hydroxy-3'-iodo-4'-ethoxy-5'-bromo phen-l'-yl)-5-substituted phenyl-2-isoxazoline (0.01 mol), phosphorus pantasulfide (P_2S_5) (0.01 mol) was refluxed in pyridine (20 mL) for *ca.* 2-3 h. The reaction mixture was cooled and diluted with water. Separated solid was filtered and crystallized from pyridine as brownish needles. The physical data of the synthesized compounds are given in Table-1.

TABLE-1
PHYSICAL CONSTANTS OF SYNTHESIZED COMPOUNDS

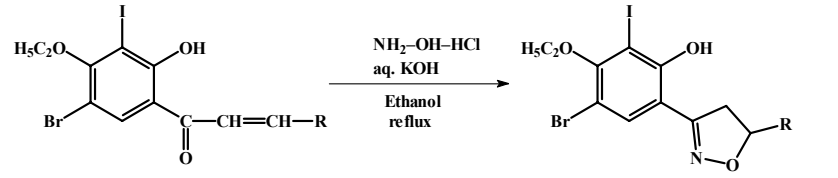
Compd. No.	R	m.f.	m.w.	m.p. (ºC)	R_f	Yield (%)	Halogen (%)	
							Calcd.	Found
1a	-C_6H_5	$C_{17}H_{15}NO_3BrI$	488.0	145	0.53	56	42.41	42.42
1b	-4-Cl-C_6H_4	$C_{17}H_{14}NO_3ClBrI$	522.5	160	0.70	55	46.40	46.43
1c	-4-OCH_3-C_6H_4	$C_{18}H_{17}NO_4BrI$	518.0	145	0.71	58	39.95	39.95
1d	-4-OH-C_5H_4	$C_{17}H_{15}NO_4BrI$	504.0	160	0.58	56	41.06	41.08
1e	-3-C_2H_5-4-OH-C_6H_3	$C_{19}H_{19}NO_4BrI$	532.0	150	0.59	56	38.90	38.92
1f	-3-NO_2-C_6H_4	$C_{17}H_{14}N_2O_5BrI$	533.0	123	0.68	54	38.82	38.83
1g	-2-NO_2-C_6H_4	$C_{17}H_{14}N_2O_5BrI$	533.0	130	0.67	58	38.82	38.84
1h	-C_4H_3O (furfuryl)	$C_{15}H_{13}NO_4BrI$	478.0	105	0.74	56	43.29	23.28
1i	-3-Br-C_6H_4	$C_{17}H_{14}NO_3Br_2I$	567.0	122	0.68	58	50.60	50.62
2a	-C_6H_5	$C_{17}H_{15}NO_3SBrI$	504.0	118	0.63	50	41.06	41.08
2b	-4-Cl-C_6H_4	$C_{17}H_{14}NO_2SClBrI$	538.5	140	0.62	45	45.02	45.00
2c	-4-OCH_3-C_6H_4	$C_{18}H_{17}NO_3SBrI$	534.0	132	0.59	50	38.76	38.78
2d	-4-OH-C_6H_4	$C_{17}H_{15}NO_3SBrI$	520.0	135	0.70	48	39.80	39.82
2e	-3-C_2H_5-4-OH-C_6H_3	$C_{19}H_{19}NO_3SBrI$	548.0	132	0.55	46	37.76	37.78
2f	-3-NO_2-C_6H_4	$C_{17}H_{14}N_2O_4SBrI$	549.0	168	0.62	50	37.70	37.72
2g	-2-NO_2-C_6H_4	$C_{17}H_{14}N_2O_4SBrI$	549.0	142	0.65	50	37.70	37.72
2h	-C_4H_3O (furfuryl)	$C_{15}H_{13}NO_3SBrI$	494.0	125	0.69	48	41.89	41.90
2i	-3-Br-C_6H_4	$C_{17}H_{14}NO_2SBr_2I$	538.0	140	0.59	46	49.22	49.25

2e: IR (KBr, ν_{max}, cm^{-1}): 3379 (Ar-OH), 2901 (C-H), 1630 (C=N), 1070 (C-N), 665 (C-Br), 567 (C-I), 611 (C-S). **2i:** NMR (δ ppm.): 1.48-1.52 (t, 3H), 4.10-4.22 (q, 2H), 3.13-3.20 (dd, 1H) 3.57-3.66 (dd, 1H), 5.60 (dd, 1H), 5.45 (s, 1H) 7.12-7.32 (m, 5H). **2h:** mass (m/z): 494 (m + 1)

Antimicrobial activity: The antibacterial activity of the synthesized compounds was screened by cup borer method[9]. The test contained 50 µg compound. The activity was screened against gram positive bacteria *S. aureus* and *B. subtilis* and gram negative bacteria *E. coli* and *S. typhii*. Similarly, the antifungal activity of the compounds was also screened by cup borer method and the test contained 100 µg compound. The activity was shown against fungul *A. niger*.

RESULTS AND DISCUSSION

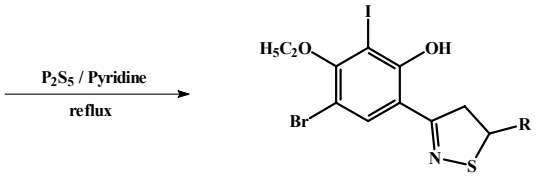
The substituted phenyl chalcone on reaction with hydroxylamine hydrochloride in presence of ethanolic KOH produce 3-(2'-hydroxy-3'-iodo-4'-ethoxy-5'-bromo phen-l'-yl)-5-substituted phenyl-2-isoxazolines [**1a-i**] and exhibits characterize peaks around 1622 cm^{-1} (C=N), 1550 cm^{-1} (N-O) and 1085 cm^{-1} (C-O) in IR spectra. Further reaction take place by P_2S_5 to produce 3-(2'-hydroxy-3'-iodo-4'-ethoxy-5'-bromo phen-l'-yl)-5-substituted phenyl 2-isothiazoline (**Scheme-I**). Compounds **2a-i** shows the IR frequency around of 1630 cm^{-1} (C=N), 610 cm^{-1} (C-S).



2'-Hydroxy-3'-iodo-4'-ethoxy-5'-bromo substituted phenyl chalcone

3-(2'-Hydroxy-3',5'-di iodo-4'-ethoxy-5'-bromo phen-1'-yl-5-substituted phenyl 2-isoxazoline

[1a-i]



3-(2'-Hydroxy-3',5'-di iodo-4'-ethoxy-5'-bromo phen-1'-yl-5-substituted phenyl 2-isothiazoline

[2a-i]

R = $-C_6H_5$, 4-Cl-C_6H_4, 4-OCH_3-C_6H_4, 4-OH-C_6H_4, 4-C_2H_5 4-OH-C_6H_3, 3NO_2-C_6H_4, 2-NO_2-C_6H_4, $-C_4H_3O$, 3Br-C_6H_4

Scheme-I

In NMR spectrum of isoxazoline, isothiazoline and its derivative resonance due to two protons attached to C-4 and one attached to C-5 of isoxazoline and isothiazoline ring showed up in form of three doublets, exhibiting a typical splitting pattern of ABX system of protons. The first doublet of doublet observed at 3.00-3.20 δ ppm was assigned, to HA, signal due to HB also appear as doublet of doublet at around at 3.45-3.70 δ ppm. Signal due to third proton of isoxazoline and isothiazoline also showed up as a doublet of doublet observed at 5.40-5.70 δ ppm. attributed Hx.

Most of these compounds were shown moderately active against bacterial spices *viz.*, gram-positive *S. aureus, B. subtilis* and gram-negative *E. coli*. Only compounds (**1a-c**) shown very poor activity against gram-negative bacteria *S. typhi* and isothiazoline are found inactive against gram-negative *S. typhi*. The antimicrobial activity revealed that compounds (**1c**, **lg**, **2f**, **2g**) were found moderately active against *S. aureus* compound **1b** and **2g** were more active against *B. subtilis*, while

compounds **1b**, **li** and **2i** were found more active against *E. coli*. All the tested compounds were found poor active (11-15 mm) against fungi *A. niger* (Table-2).

TABLE-2
ANTIMICROBIAL ACTIVITY OF SYNTHESIZED COMPOUNDS

Compd. No.	Zone of inhibition (mm)				
	Antibacterial activity				Fungicidal activity
	S. aureus	*B. subtilis*	*E. coli*	*S. typhi*	*A. niger*
1a	10	12	14	9	10
1b	11	17	17	9	10
1c	18	11	11	9	12
1d	13	15	14	–	11
1e	13	12	14	–	12
1f	12	13	13	–	14
1g	16	14	13	–	13
1h	12	11	13	–	11
1i	13	11	17	–	10
Standard drugs					
Amoxicillin	22	23	24	24	–
Ciprofloxacin	26	25	24	25	–
Griseofulvin	–	–	–	–	26
2a	13	12	10	–	12
2b	13	12	14	–	12
2c	11	11	14	–	13
2d	13	11	10	–	14
2e	13	12	11	–	12
2f	16	13	14	–	14
2g	15	16	10	–	15
2h	13	11	10	–	11
2i	13	11	17	–	11
Standard drugs					
Amoxicillin	22	23	24	24	–
Ciprofloxacin	26	25	24	25	–
Griseofulvin	–	–	–	–	26

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