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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF NOVEL ISOTHIAZOLINE DERIVATIVES

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ABSTRACT

Among a wide variety of heterocycles that have been explored for developing pharmaceutically important molecule, isoxazoline and isothiazoline are one of them. Several nitrogen and sulfur containing heterocycle compounds are useful in pharmaceutical chemistry.

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. The antimicrobial activities of the synthesized compounds have been compared with standard drugs like Amoxicillin, Ciprofloxacin and Griseofulvin.

Key words: Isothiazoline derivatives, Antimicrobial activity.

INTRODUCTION

Isoxazoline and their derivatives are important chemotherapeutic agents. Isoxazolines are one of the known heterocyclic compounds, which contain nitrogen and oxygen as heteroatoms. 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 antifungalactivity[7-9].

EXPERIMENTAL

Melting points of the synthesized compounds were taken in open capillaries and are uncorrected. The 1R spectra were recorded on a Shimadzu FT1R 8400 spectrophotometer,

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PMR spectra were recorded on a BRUKER (300 MHz) spectrometer using TMS as internal standard and Mass spectra were recorded on a Jeol SX-102 (FAB) Mass spectrometer.

General procedure for the preparation of 3-(2'-hydroxy-3',5'di iodo-4'-ethoxy phen-1' yl)-5-substituted phenyl -2-isoxazoline

A mixture of 2'-hydroxy-3'-5'-di-iodo-4'-ethoxy-substituted phenyl chalcone (0.01 mole), hydroxylamine hydrochloride (0.02 mole) and aq. KOH (2 mL) was refluxed in ethanol (30 mL) for about 4 to 5 hrs. The reaction mixture was cooled and acidified by 1 : 1 HC1 in ice cold condition. Separated solid was filtered and crystallized from dilute ethanol as brownish needles.

Spectroscopic data of synthesized compound (1b, 1a, 1f)

(1b) IR (KBr) cm^{-1} : 3379 (Ar-OH), 1612 (C=N), 1082 (C-N), 3350 (N- H), 2854 (C-H), 780 (C-C1), 567 (C-I).

(1a) NMR (δ ppm.) : 1.48-1.52 (t, 3H), 4.10-4.22 (q, 2H), 8.50 (s, 1H), 3.03-3.10 (dd, 1H), 3.47-3.56 (dd, 1H), 5.33 (dd, 1H), 5.80 (s, 1H), 7.12-7.32 (m,6H).

(1f) Mass (m/z) : 580 (m+1)

General procedure for the preparation of 3-(2'-hydroxy-3',5'di iodo-4'-ethoxy phen-1' yl)-5-substituted phenyl -2- isothiazoline

A mixture of 3-(2'-hydroxy-3'-5'-di-iodo-4'-ethoxy phen-l'-yl)-5-substituted phenyl-2-isoxazoline (0.01 mole), phosphorus pantasulfide (P_2S_5) (0.01 mole) was refluxed in pyridine (20 mL) for about 2-3 hrs. The reaction mixture was cooled and diluted with water. Separated solid was filtered and crystallized from dilute pyridine as brownish needles.

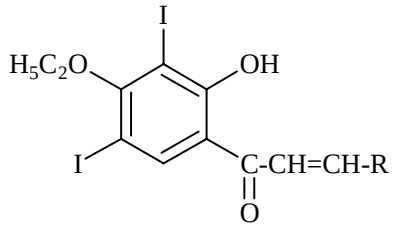
Spectroscopic data of synthesized compound (2i, 2c, 2d)

(2i) IR (KBr) cm^{-1}: 3380 (Ar-OH), 1618 (C=N), 1082 (C-N), 2850 (C-H), 608 (C-Br), 570 (C-I) 615 (C-S).

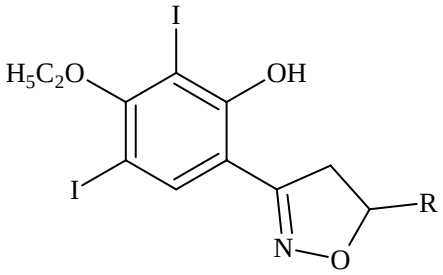
(2c) NMR (δ ppm.): 1.47-1.51 (t, 3H), 4.01-4.15 (q, 2H), 8.52 (s, 1H), 3.84 (s,-OCH_3), 3.00-3.09 (dd, lH) 3.47-3.55 (dd, 1H), 5.30 (dd, 1H), 5.80 (s, 1H), 7.12-7.32 (m, 6H).

(2d) Mass (m/z): 567 (m+1).

Reaction scheme

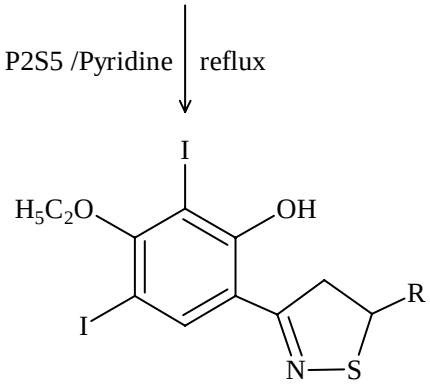


2'-hydroxy -3'-5'-iodo-4'-ethoxy substituted phenyl chalcone



3-(2'-hydroxy -3'-5'-di iodo-4'-ethoxy phen-1' yl) -5- substituted phenyl -2- isoxazoline.

(1 a-i)



3-(2'-hydroxy -3'-5'-di iodo-4'-ethoxy phen-1' yl) -5- substituted phenyl-2- isothiazoline.

(2 a-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

Antimicrobial activity

The antibacterial activity of the synthesised compounds was screened by cup borer method[10]. The test contained 50 µ.g. compound. The activity was screened against gram positive bacteria *S. aureus* and *B. subtilis* and gram negative bacteria *E. coli* and *S. typhi.* Similarly the anti fungal activity of the compounds was also screened by cup borer method and the test contained 100 µ.g. compound. The activity was screened against fungul *A. niger*. The antimicrobial activities are summarized in the Table 1 and 2.

Table 1: Physical constants of synthesized compounds

Comp. No.	R	Molecular formula	M.W.	M.P. (°C)	R_f	% of Yield	% of Halogen	
							Calcu.	Found
1a	-C_6H_5	$C_{17}H_{15}0_3NI_2$	535	137	0.69	55%	47.47	47.50
1b	-4-Cl-C_6H_4	$C_{17}H_{14}O_3NC1I_2$	569.5	150	0.65	58%	50.83	50.84
1c	-4-OCH_3-C_6H_4	$C_{18}H_{I7}0_4NI_2$	565	150	0.71	56%	44.95	44.96
1d	-4-OH-C_5H_4	$C,_7H,_50_4NI_2$	551	160	0.73	55%	46.09	46.12
1e	-3-C_2H_5-4-OH-C_6H_3	$C_{19}H,_90_4NI_2$	579	167	0.59	54%	43.86	43.88
1f	-3-$N0_2$-C_6H_4	$C_{I7}H_{14}0_5N_2I_2$	580	114	0.63	58%	43.79	43.83
1g	-2-NO_2-C_6H_4	$C_{I7}H,_40_5N_2I_2$	580	85	0.72	56 %	43.79	43.82
1h	-C_4H_3O (furfuryl)	$C_{15}H_{13}0_4N1_2$	525	100	0.75	55%	48.38	48.38
1i	-3-Br-C_6H_4	$C_{17}H_{14}O_3NBrI_2$	614	138	0.69	58%	54.38	54.36

Table 2: Physical constants of synthesized compounds

Comp. No.	R	Molecular formula	M.W	M.P. (°C)	R_f	% of Yield	% of Halogen	
							Calcu.	Found
2a	-C_6H_5	$C_{17}H_{15}0_2NI_2S$	551	152	0.52	45%	46.09	46.10
2b	-4-Cl-C_6H_4	$C_{17}H_{14}O_2NC1_{12}S$	585.5	125	0.51	50%	49.44	49.46
2c	-4-OCH_3-C_6H_4	$C_{18}H_{I7}0_3NI_2S$	581	168	0.49	48%	43.71	43.72
2d	-4-OH-C_6H_4	$C_{17}H_{15}0_3NI_2S$	567	142	0.58	46%	44.79	44.80
2e	-3-C_2H_5-4-OH-C_6H_3	$C_{19}H_{I9}0_3NI_2S$	595	138	0.55	50%	42.68	42.70

Cont…

Comp. No.	R	Molecular formula	M.W	M.P. (^oC)	R_f	% of Yield	% of Halogen	
							Calcu.	Found
2f	-3-$N0_2$-C_6H_4	$C_{17}H,_4 0_4N_2I_2S$	596	98	0.50	45%	42.61	42.62
2g	-2-NO_2-C_6H_4	$C_{I7}H_{14}0_4N_2I_2S$	596	118	0.51	48%	42.61	42.62
2h	-C_4H_3O (furfuryl)	$C_{15}H,_3 0_3NI_2S$	541	128	0.53	50%	46.95	46.98
2i	-3-Br-C_6H_4	$C_{I7}H_{I4}O_2N$ BrI_2S	630	158	0.54	46%	53.00	53.04

TLC Solvent system : - Acetone: Benzene (3.5 : 6.5)

RESULTS AND DISCUSSION

In present study, we have conducted the reaction in presence of ethanolic KOH between substituted phenyl chalcone and hydroxylamine hydrochloride to produce 3-(2'-hydroxy -3'-5'- di- iodo-4'-ethoxy phen-1' yl) -5- substituted phenyl 2- isoxazoline **(1 a-i)**. It is further taken for the next step with Pyridine / P_2S_5 to produce 3-(2'-hydroxy -3'-5'- di- iodo -4'-ethoxy phen-1' yl) -5- substituted phenyl 2- isothiazoline **(2 a-i)**. The structures of newly synthesized compounds **(1 a-i)** and **(2 a-i)** were investigated according to their analytical and spectral data. The synthesized compounds were under taken for the anti microbial activity and results were dictated in the Table 3 and 4.

Table 3: Antimicrobial activity of synthesized compounds (1 a-i)

Comp. No.	Antibacterial activity (Zone of inhibition in mm)				Fungicidal activity (Zone of inhibition in mm)
	S. aureus	***B. subtilis***	***E. coli***	***S. typhi***	***A. niger***
1a	12	11	13	14	13
1b	13	11	13	12	16
1c	19	11	18	12	11
1d	12	14	13	11	14
1e	13	14	13	11	13
1f	14	15	13	12	11
1g	16	15	13	13	17
1h	13	14	14	12	16
1i	19	14	13	14	12

Cont…

Comp. No.	Antibacterial activity (Zone of inhibition in mm)				Fungicidal activity (Zone of inhibition in mm)
	S. aureus	***B. subtilis***	***E. coli***	***S. typhi***	***A. niger***
Standard drugs					
Amoxicillin	22	23	24	24	-
Ciprofloxacin	26	25	24	25	-
Griseofulvin	-	-	-	-	26

Table 4: Antimicrobial activity of synthesized compounds (2 a-i)

Comp. No.	Antibacterial activity (Zone of inhibition in mm)				Fungicidal activity (Zone of inhibition in mm)
	S. aureus	***B. subtilis***	***E. coli***	***S. typhi***	***A. niger***
2a	12	11	11	12	12
2b	12	11	12	12	12
2c	19	12	11	12	13
2d	13	12	11	13	13
2e	13	11	12	14	12
2f	13	12	12	14	11
2g	16	12	15	NA	11
2h	13	11	19	NA	12
2i	13	12	12	NA	12
Standard drugs					
Amoxicillin	22	23	24	24	-
Ciprofloxacin	26	25	24	25	-
Griseofulvin	-	-	-	-	26

The IR spectra of synthesized compounds showed characteristic bands, which were assigned in accordance with literature data. The absorption bands assignable to the stretching of C=N bond for compounds **(1 a-i)** were observed at frequencies range of 1612-1625 cm^{-1}.

A band assignable to the stretching of -N-O and -C-O exhibits characterize peaks around 1550 cm^{-1} and 1085 cm^{-1}, respectively. In IR Spectra of 3-(2'-hydroxy-3'- -5'-di-iodo-4'-ethoxy phen-1' yl) -5- substituted phenyl 2-isothiazoline **(2 a-i)** shows characteristic bands around the range of 1618 cm^{-1} (C=N), 615 cm^{-1} (C-S). In the both compounds Ar-OH shows the broad band at 3395-3450 cm^{-1}.

The ^1H NMR data recorded in $CDCl_3$. Spectrum of isoxazoline and isothiazoline 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. A doublet appeared as a doublet at 3.03-3.10 δ ppm can be considerable due to H_A isoxazoline and isothiazoline ring. Signal due to H_B also appear as doublet of doublet at around at 3.45-3.55 δ ppm. Signal due to third proton of isoxazoline and isothiazoline also showed up as a doublet of doublet observed at 5.30-5.40 δ ppm. attributed H_X. All of the possible fragmentations peaks are observed from the MASS spectrum analysis, as expected.

Isoxazoline, isothiazoline and its derivatives showed the broad spectrum of antimicrobial activity. The activity spectrum showed that most of these compounds were moderately active against bacterial spices viz gram-positive *S. aureus, B. subtilis* and gram-negative *E.coli.* The anti microbial activity revealed that compounds (**1c**, **1g**, **1i**, **2c**, **2g**) were found moderately active against *S. aureus.* All compounds were found poor active against *B. subtilis*. While compound no **1c** and **2h** were more active against *E. Coli*. Compounds **(1 a-i)** shown moderate activity against gram-negative bacteria *S. typhi.* and isothiazoline **(2 a-f)** were found poor active against gram-negative *S. typhi.* All the tested compounds were found poor active (11-15 mm zone of inhibition) against fungi *A. niger*.

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