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SYNTHESIS AND ANTIMICROBIAL SCREENING OF CERTAIN SUBSTITUTED CHALCONES AND ISOXAZOLINES BEARING HYDROXY BENZOFURAN

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ABSTRACT

3-Hydroxy Bezofuran Chalcones (2a-g) prepared by the reaction of 2-acetyl-3-hydroxybenzofuran(1) with different aromatic aldehydes in the presence of a strong base, cyclocondensation of 3-Hydroxy benzofuran with hydroxlaminehydrochloride resulted in the formation of various Isoxazolines bearing hydroxyl benzofuran (3a-f). The structures of all the compounds have been established on the basis of analytical and spectral data. All the compounds have screened for antibacterial, while compounds 2a,2c,3a,3b, showed only moderate activity against staphylococcus at 500 mg/ml, compounds 2d, 2f, 3d, 3e, showed promising activity against Candida albicans at 500mg/ml concentration.

Keywords: *Hydroxy Benzofuran Chalcones, Hydoxylaminehydrochloride, Isoxazolines, Antimicrobial activity.*

INTRODUCTION

Nitrogen and oxygen containing heterocyclic compounds have received considerable attention due to there wide range of pharmacological activity. Isoxazolines represent one of the active classes of compounds possessing a wide spectrum of biological activities. Isoxazolines have been reported to possess antidiabetic[1,] diuretic[2],analgesic[3,] , anthelimentic[4], hypolipaemic[5,] and antimicrobial activity[6].

The biological significance of this heterocycle has received considerable attention in recent years[7]. Benzofuran derivatives, which are known to be present in many natural products [8,] have physiological, pharmacological and toxic properties and find application has sedative, hypnotics[9], antibacterial [10] and antifungal activities [11.]In search of newer potential drugs, coupling of isoxazoline ring with other bioactive heterocycles has been a most common approach in many laboratories. Many heterocyclic analogous of chalcones have been synthesized and subsequently demonstrated to possess biological and pharmacological activities, which may possibly result in chemotherapeutic agents. Because of great synthetic potentiality the heterocyclic analogous of chalcones are most useful synthons. Hence it was thought of modifying chemically benzofuran analogous of chalcones into isoxazole ring system so as to produce biheterocyclic Benzofuryl isoxazoles.

The required starting material 2-acetyl -3 hydroxy benzofuran (1) was prepared by a single step method. This method involves the condensation of Methyl salicylate with Chloroacetone in anhydrous acetone in presence of anhydrous potassium carbonate at reflux temperature. The treatment of ethanolic solution of 2-acetyl – 3 hydroxy benzofuran and aromatic aldehyde with 50% aqueous sodium hydroxide at 5-10 ^{o} c led to the formation of 1-(3^{1}- hydroxy benzofuran-2^{1}–yl)–3- aryl – 2- propene –1- one(2a –g) in yields ranging from 40-89%. The structures of Benzofuran analogous of Chalcones were confirmed chemically by there conversion into 2-4-

dinitrophenyl hydrazones and also on the basis of spectroscopic data. The I.R spectrum of compounds 2a-g exhibited a broad hump in the region of 3400- 3450 cm $^{-1}$ (OH), sharp band in the region of 1650-1660 cm $^{-1}$(C= O) due to the α, β, unsaturated carbonyl group and a series of bands in the region of 1640-1560 cm -1(C=C) due to the aromatic side chain groups. In the ^{1}H NMR spectrum ($CDCl_3$) doublets at δ 8.40 (1H, C=CH – Ar), δ 6.76-7.74(10H, Ar-H) and δ 6.60(1H, COCH =C) δ 8.3-8.9(OH) were observed. The synthesis of biheterocyclic isoxazolenyl benzofurans using this hydroxy benzofuran chalcones was accomplished by reacting with hydroxylamine hydrochloride in presence of freshly fused sodium acetate in ethanolic solution at reflux temperature. The various 3-(3^1 –hydroxy benzofuran -2^1-yl)-5-aryl-isoxazalines (3 a-f) were obtained in a yield ranging from 29-30%. The negative ferric chloride test indicates the formation of isoxazolenyl ring system. This was further evident by spectral data. The IR spectra of(3 a-f) revealed the absence of α, β unsaturated carbonyl group indicating involvement of this functionality in the formation of isoxazoline ring a broad hump in the region of 3400-3450 cm^{-1}(OH), a characteristic absorption band at 1610cm(C=N) due to C=N of isoxazoline. The ^{1} H NMR spectrum of 3a was recorded it displayed two doublets of doublets due to CH_2 protons of isoxazoline moiety at δ 2.63 and 2.78 and 3.6 ppm due to –CH protons.

EXPERIMENTAL

Melting points were determined with open capillary and are uncorrected. I.R spectra were recorded on a Shimadza FTIR model 8010 spectrophotometer, ^{1}H NMR spectra were recorded in $CDCl_3$ on aBruker supercon FT-NMR instrument using TMS as internal standard.

General Procedure for the synthesis of 1-(3- hydroxy benzofuran -2- yl) – 3- aryl – 2- propene – 1 – ones (2a-h)

A solution of 2-acetyl -3-hydroxy benzofuran (0.85g, 0.005mole) and aromatic aldehyde (0.005mole) in ethanol (12ml) was cooled to 5-10°C in an ice bath. The cooled solution was treated with drop wise addition of aqueous sodium hydroxide (2.5ml, 70%). The reaction mixture was magnetically stirred for 30minutes and then left overnight. The resulting dark solution was diluted with ice water and carefully acidified using dilute hydrochloric acid. The hydroxy benzofuran analogue of chalcone which separated as a solid was collected by filtration after washing with sodium bicarbonate and water. It was further purified by crystallization from suitable solvent.

General procedure for the synthesis of 3-(3^1 –hydroxy benzofuran-2^1 –yl)-5- aryl – isoxazolines: (3a-f)

1-(3- hydroxy benzofuran -2- yl) – 3- aryl – 2- propene – 1 – one (0.005mole) was dissolved in ethyl alcohol (15ml). Hydroxylamine hydrochloride (0.3g) and freshly fused anhydrous sodium acetate (3.0g) were added to this solution. The reaction mixture was heated under reflux for 7hrs in a water bath. The content of the flask was poured in to ice water with stirring. The isoxazoline which separated as a solid was filtered washed with water and dried. Further purification was done by crystallization using suitable solvent. Characterization data of the synthesized compounds are reported in table-1

1-(3-hydroxy benzofuran-2-yl)-3-(4-Chlorophenyl)-2-propene-1-one (2c)
IR: 1650(C=0), 1630(C=C), 1080 (C-O-C) and 3400 cm^{-1}(-OH);
^{1}H NMR ($CDCl_3$): δ 6.70- 7.70 (m, 9H, Ar-H), 6.60(d, 1H, -COCH=), 8.60(d, 1H, =CH-Ar), 8.9(s,1H,-OH),

1-(3-hydroxy benzofuran-2-yl)-3-(4-Nitrophenyl)-2-propene-1-one (2d)
IR: 1655 (C=O), 1620(C=C), 1090(C-O-C) and 3410 cm^{-1} (-OH);
^{1}H NMR ($CDCl_3$): δ 6.68- 7.00 (m, 9H, Ar-H), 6.40(d, 1H, -COCH=), 8.40(d, 1H, =CH-Ar), 8.7(s,1H,-OH),

1-(3-hydroxy benzofuran-2-yl)-3-(4-Methoxyphenyl)-2-propene-1-one (2e)
IR: 1660(C=O), 1618(C=C), 1092(C-O-C) and 3410 cm^{-1} (-OH);
^{1}H NMR ($CDCl_3$): δ 6.70- 7.80 (m, 9H, Ar-H), 6.50(d, 1H, -COCH=), 8.20(d, 1H, =CH-Ar), 8.4(s,1H,-OH),

3-(3^1- Hydroxy benzofuran-2^1-yl) -5-(4-Hydroxyphenyl) Isoxazoline. **(3a)**
IR: 1600(C=C), 1618 cm^{-1}(C=N); ^{1}H NMR ($CDCl_3$): δ 2.5-3.1(dd, -CH_2 -), 3.6(t,CH), 6.68-7.70(m, 9H, Ar-H), 8.3(s,1H,-OH),

3-(3^1- Hydroxy benzofuran-2^1-yl) -5-(4-Methoxyphenyl) Isoxazoline. (3b)
IR: 1610(C=C), 1620 cm^{-1}(C=N); ^{1}H NMR ($CDCl_3$): δ 2.4-3.3(dd, -CH_2 -), 3.6(s,-OCH_3), 3.3(t,CH), 6.60-7.70(m, 9H, Ar-H), 8.5(s,1H,-OH),

Antimicrobial activity:
All the newly synthesized compounds were screened for antimicrobial activity against both gram positive S.aureus and gram negative E.coli bacteria and antifungal activity against C.albicans and A.flavus according to cup plate method [12] at a concentration of 0.005 mole/ml. Streptomycin and Gressofulvin were used as standard for comparison of antibacterial[13] and antifungal activity[14]. Solvent DMF was used as control. The results of screening are given in table 2 and 3

RESULTS AND DISCUSSION

The structures of the compounds were confirmed by the analytical and spectral data.
Out of the 13 compounds screened for antibacterial activity none of them possessed appreciable activity against both the types of bacteria. Most of the compounds are very weakly active and a few were moderately active.
Amongst the 11 compounds screened for antifungal activity **2e, a** benzofuran analogue of chalcone has shown antibacterial activity almost equal to those of standards against both the type of fungi. Compounds **2c, 2d, 3d** and **3e** possess very good activity only against *Aspergillus flavus and the* compound **2b** was also considerably active.

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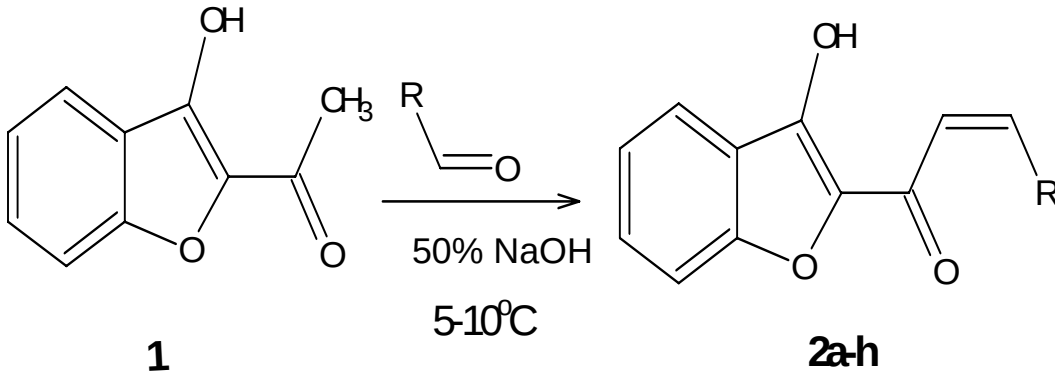
TABLE – 1:Characterization data of compounds

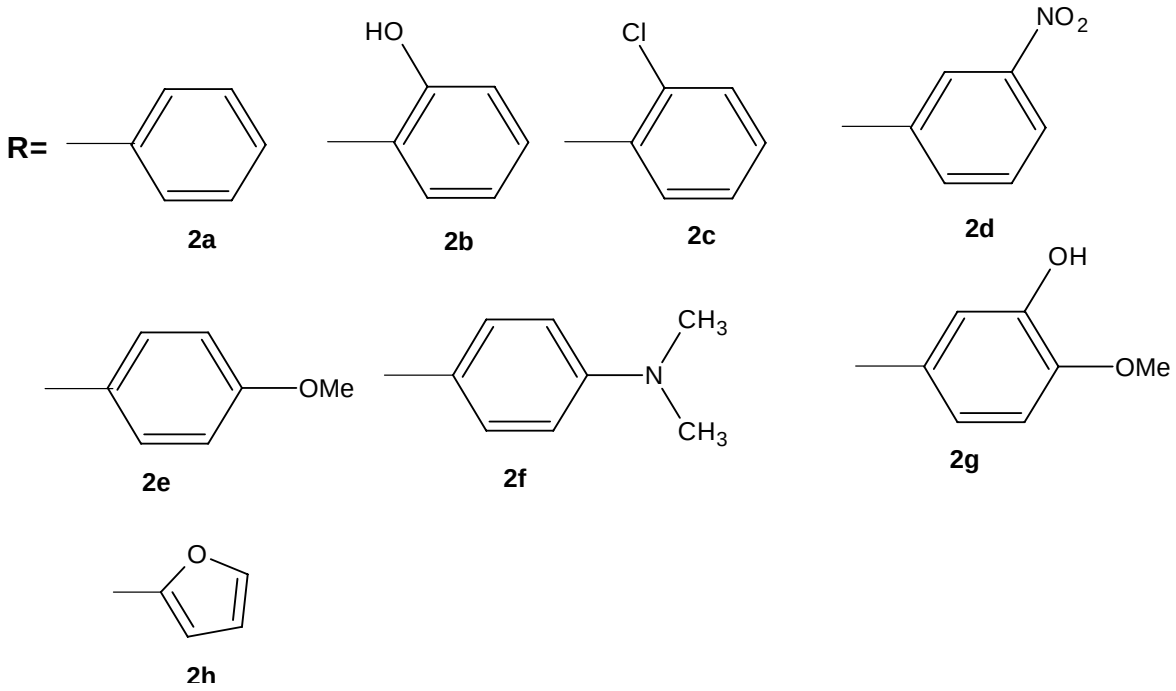
Compound	R	Mol. Formula	%Yield	M.P (°C)	Found (Calcd) %		
					C	H	N
2a	H	$C_{17}H_{12}O_3$	62	80	72.31 (72.27)	4.65 (4.54)	-
2b	OH	$C_{17}H_{12}O_4$	51	75	73.01 (72.85)	4.44 (4.28)	
2C	Cl	$C_{17}H_{11}O_3Cl$	56	134	68.57 (68.45)	3.81 (3.69)	
2d	NO2	$C_{17}H_{11}NO_5$	72	75	66.20 (66.01)	3.71 (3.55)	44.76 (4.85)
2e	OCH_3-	$C_{18}H_{14}O_4$	45	62	73.51 (73.46)	4.71 (4.76)	
2f	-N<	$C_{19}H_{17}NO_3$	67	110	74.15 (74.26)	5.61 (5.53)	4.71 (4.73)
2h	C_4H_3O	$C_{15}H_{10}O_4$	89	78	71.01 (70.86)	4.08 (3.93)	
3a	OH	$C_{17}H_{11}No_4$	50	110	69.77 (69.62)	3.81 (3.75)	4.63 (4.70)
3b	OCH_3	$C_{18}H_{13}NO_4$	33	70	70.41 (70.35)	4.28 (4.23)	4.65 (4.56)
3c	NO_2	$C_{17}H_{10}N_2O_6$	33	110	65.71 (65.68)	3.36 (3.26)	4.71 (8.68)
3d	N-$(CH_3)_2$	$C19H_{16}N_2O_3$	50	120	71.37 (71.25)	5.11 (5.00)	4.81 (8.75)
3e	OH–OCH_3	$C_{18}H_{13}NO_5$	29	83	66.92 (66.87)	4.04 (4.02)	4.53 (4.02)
3f	C_4H_3O	$C_{15}H_9NO_4$	29	68	67.61 (67.41)	6.47 (8.37)	5.34 (5.24)



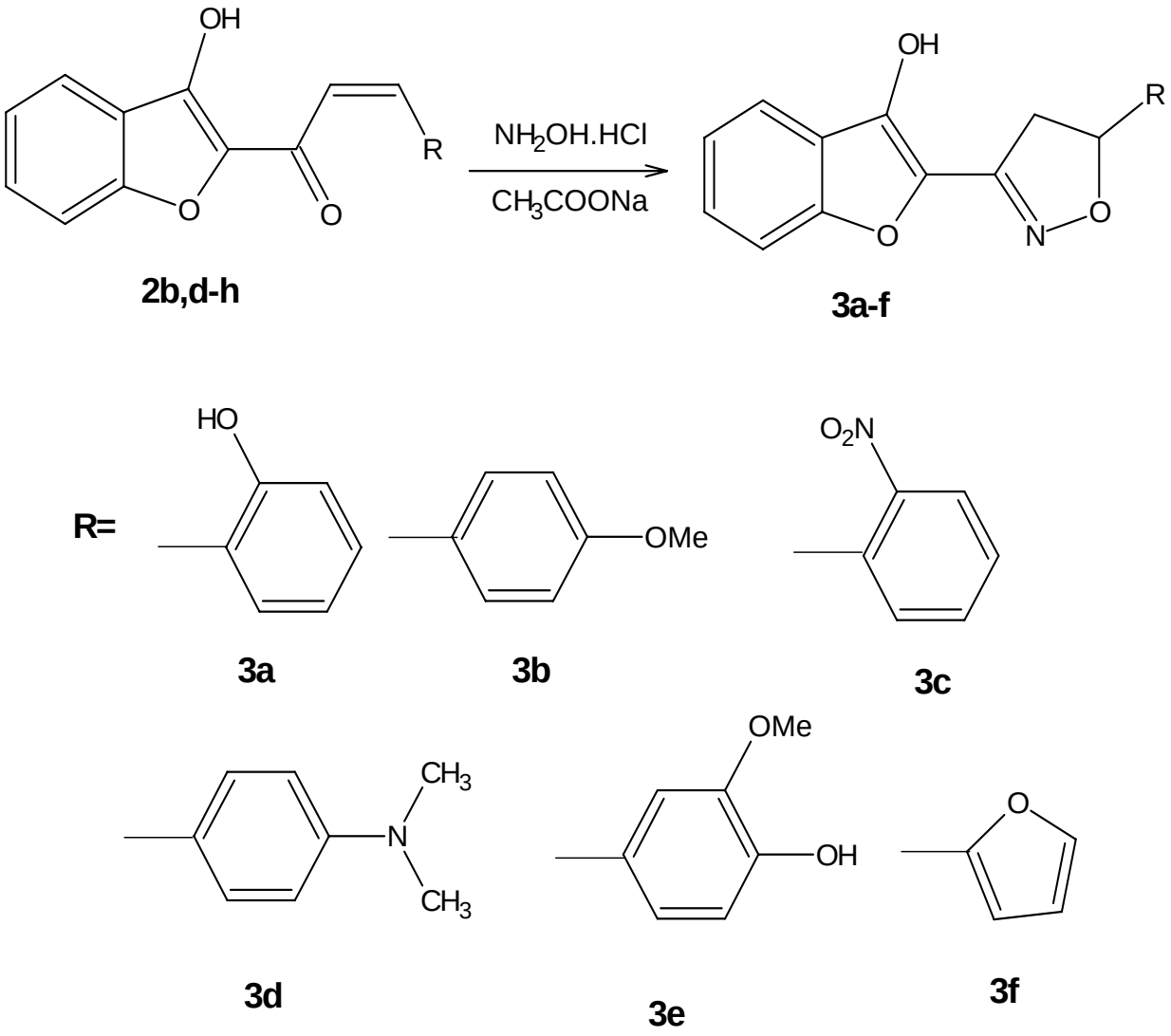
1 **2a-h**

Scheme-1

Where, R=



2a **2b** **2c** **2d** **2e** **2f** **2g** **2h**



Scheme-2

Table –2:Antibacterial activity

Sl. No	Name of the compounds	*Mean zone of inhibition (in mm)*			
		Staphylococcus aureus		***Escherichia coli***	
		50μg	**100μg**	**50μg**	**100μg**
01	Procaine penicillin	19	23	-	-
02	Streptomycin	-	-	20	24
03	2 a	12 mm	15 mm	9 mm	12 mm
04	2 b	13 mm	15 mm	8 mm	10 mm

05	2 c	14 mm	16 mm	11 mm	12 mm
06	2 d	12 mm	15 mm	7 mm	11 mm
07	2 e	11 mm	14 mm	8 mm	10 mm
08	2 f	15 mm	17 mm	9 mm	12 mm
09	2 g	13 mm	14 mm	8 mm	9 mm
10	2 h	13 mm	15 mm	10 mm	9 mm
11	3 a	13 mm	16 mm	08 mm	12 mm
12	3 b	12 mm	18 mm	07 mm	11 mm
13	3 c	13 mm	16 mm	10 mm	11 mm
14	3 d	14 mm	18 mm	08 mm	10 mm
15	3 e	13 mm	17 mm	09 mm	12 mm

Table-3 :Antifungal activity

Sl. No	**Name of the compounds**	**Mean zone of inhibition (in mm)**			
		Candida albicans		***Asperagillus flavus***	
		50μg	**100μg**	**50μg**	**100μg**
01	Griseofulvin	21	24	21	24
02	2 a	13 mm	16 mm	12 mm	15 mm
03	2 b	18 mm	21 mm	17 mm	21 mm
04	2 c	18 mm	20 mm	16 mm	22 mm
05	2 d	12 mm	15 mm	19 mm	22 mm
06	2 e	19 mm	22 mm	20 mm	22 mm
07	2 f	14 mm	16 mm	14 mm	15 mm
08	3 a	10 mm	11 mm	11 mm	16 mm
09	3 b	14 mm	15 mm	16 mm	19 mm
10	3 c	11 mm	14 mm	12 mm	15 mm
11	3 d	12 mm	14 mm	20 mm	23 mm
12	3 e	15 mm	18 mm	19 mm	22 mm