Int. J. Chem. Sci.: 6(1), 2008, 351-357

SYNTHESIS OF SOME 3-ARYL-2-(5'-CHLORO-3'-METHYLBENZOFURAN-2'-YL)-1, 4-QUINOXALYL METHANES OF BIOLOGICAL INTEREST

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ABSTRACT

Some new series of benzofuran quinoxaline derivatives **(12-16)** were prepared from benzofuran analogues of dibromo chalcones **(7-11)** by treatment with orthophenylene diamine in dry toluene. These compounds were screened for *in vitro* antibacterial and antifungal activities.

Key words: Benzofuran quinoxaline, α, β-Dibromoderivatives of chalcones, Antibacterial, Antifungal.

INTRODUCTION

Quinoxalines are the heterocyclic compounds, which have been found to exhibit biological activities such as antibiotic, antibacterial, antifungal, antiviral, anticancer and antihelminthic activity[1-6]. In view of the above facts, above title compounds containing quinoxaline ring system coupled with naturally occurring and physiological active benzofuran moiety have been synthesized[7-11] in expectation to enhance their biological activities.

In the present work, the use of α,β-unsaturated ketones of benzofuran in the synthesis of benzofuran quinoxaline via α,β-dibromo derivatives of benzofuran analogues of chalcones has been described. The benzofuran analogues of chalcones[12-15] **(2-6)** were prepared from 5-chloro-3-methyl-2-acetylbenzofuran[12]condensation with aromatic aldehydes in ethanol in presence of strong alkali.

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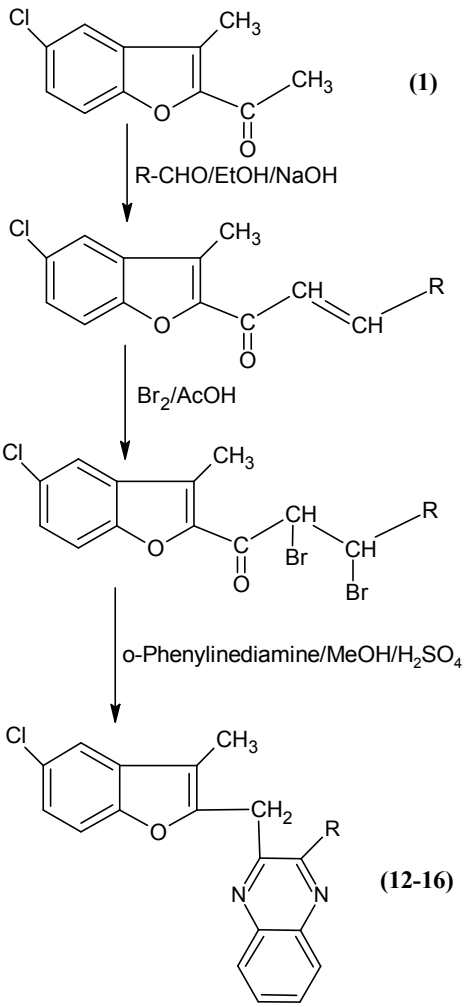

Scheme 1

Benzofuran analogues of chalcones **(2-6)** were further converted into α, β-dibromo derivatives of benzofuran analogues of chalcones **(7-11)** by bromination. The reaction of compounds **(7-11)** with orthophenylenediamine in methanol in presence of catalytic quantity of sulphuric acid to gave corresponding 3-aryl-2-(5`-chloro-3`-methylbenzofuran-2'-yl)-1,4-quinoxalyl methanes **(12-16)**.

The structures of newly synthesized compounds were assigned on the basis of IR,

^{1}H NMR, mass spectra and elemental analysis. All compounds were screened for *in vitro* antibacterial and antifungal activity and results are presented.

Antibacterial activity

Compounds synthesized during present work were screened for their antibacterial activity using cup-plate diffusion method[16]. The organism selected such as *S. aureus* and *E. coli* were procured from Department of Microbiology, Gulbarga University, Gulbarga. All the compounds tested at the concentration of 100 μg/0.1 mL. Ciprofloxacin was used as standard drug. The zone of inhibition for all compounds were recorded after 24 h of incubation at optimum temperature.

Compounds **(7)**, **(9)** and **(11)** were showed good antibacterial activity against *S. aureus* and *E. coli,* when compared with standard drug. Remaining compounds exhibited moderate activity against bacteria.

Antifungal activity

Compounds **(7-16)** evaluated for fungicidal activity using *A. niger* and *C. albicans* by cup-plate diffusion method. All the compounds prepared and used at the concentration of 100 μg/0.1mL in DMF using griseofulvin used as standard drug. The zone of inhibition were recorded after 24 h at 37^{o}C. Compounds **(7), (8), (9)** and **(10)** showed marked antifungal activity against *A. niger* and *C. albicans*. Other compounds exhibited moderate activity against both fungi, when compared with the standard drug.

The *in vitro* antibacterial and antifungal activity results are reported in Table 2.

EXPERIMENTAL

All the reagents and solvents used were of laboratory grade. The purity of the compounds was determined by TLC using suitable solvent system. The IR spectra were recorded in KBr on FT IR-1000 spectrophotometer. The ^{1}H NMR spectra were recorded on JEOL model DSX-300/AMX-400/DRX-500 FT NMR spectrophotometer in $CDCl_3$ using TMS as internal standard. The mass spectra were recorded on GC-MASS SPEC PINNIGAN MAT 823MS mass spectrophotometer. Melting points of all synthesized compounds were determined in open glass capillary tubes and are uncorrected.

5-Chloro-3-methyl-2-acetylbenzofuran (1)

To a solution of 5-chloro-2-hydroxyacetophenone **(2)** (4.26 g, 0.025 mol)

anhydrous acetone (35 mol), chloroacetone (2.31g, 0.025 mol) and anhydrous carbonate (7.5 g) were added. The reaction mixture was heated under gentle reflux for 12 h. Then it was cooled, potassium salts were filtered off and washed with acetone. The excess of acetone was removed under reduced pressure and the resulting oil solidified on cooling. The solid obtained was collected and crystallized from benzene (3.82 g, 74%) m.p. 104^0C.

IR (KBr) cm^{-1}: 3050(C-H str. Ar), 2900(C-H, str. methyl), 1674 (C=O), 1573 (C=C). ^{1}H NMR ($CDCl_3$) δ ppm 2.5 (s, 3H, CH_3), 2.6(s, 3H, $COCH_3$), and 7.4-7.6 (m, 3H, Ar-H). Mass spectra m/z 208, 210(M^+, M^{+2}) and other prominent peaks are 193, 195,165, 137, 102, 75 and 51.

5-Chloro-3-methyl-2-phenylideneacetylbenzofurans (2)

To a mixture of 5-chloro-3-methyl-2-acetyl benzofuran **(1)** (2.08 g, 0.01 mol) and benzaldehyde aldehyde (0.001 mol) in ethanol (25 mL) cooled at 5-10^0C aqueous sodium hydroxide (70%, 2.5 mL) was added dropwise with constant stirring.

Table 1. Physical data of compounds (7-16)

Comp.	R	Yield (%)	M. P. (ºC)	Solvent of crystallization	Molecular formula
(7)	C_6H_5	69	170	Ethanol	$C_{18}H_{13}O_2Br_2Cl$
(8)	C_6H_4OH (o)	63	145	Benzene	$C_{18}H_{13}O_3Br_2Cl$
(9)	C_6H_4OH (p)	70	233	Ethanol	$C_{18}H_{13}O_3Br_2Cl$
(10)	$C_6H_4OCH_3$ (p)	60	120	Ethanol	$C_{19}H_{15}O_3Br_2Cl$
(11)		66	135	Ethanol	$C_{16}H_{11}O_3Br_2Cl$
(12)	C_6H_5	80	170	Ethanol	$C_{24}H_{17}ON_2Cl$
(13)	C_6H_4OH (o)	78	172	Ethanol	$C_{24}H_{17}O_2N_2Cl$
(14)	C_6H_4OH (p)	62	235	Ethanol	$C_{24}H_{17}O_2N_2Cl$
(15)	$C_6H_4OCH_3$ (p)	72	130	Ethanol	$C_{25}H_{19}O_2N_2Cl$
(16)		70	163	Ethanol	$C_{22}H_{15}O_2N_2Cl$

C, H and N analysis gave satisfactory results.

The reaction mixture was stirred further for 2 h and left overnight. The reaction mixture was neutralized with concentrated hydrochloric acid, the solid then separated was collected and crystallized from ethanol. Yield 68%, m.p 130ºC, IR (KBr) cm^{-1} 3060(C-H, Str. Ar), 2920 (C-H, str. CH3), 1651(C=O), 1596(C=C). 1HNMR ($CDCl_3$) δ ppm 2.4(d, 1H, -C=CH-Ar), 2.6(s, 3H, CH3), 3.5(d, 1H, -COCH-C) and 7.4-7.9(m, 8H, Ar-H). Similarly other compounds **(3-6)** of the series were prepared (Table 1).

5-Chloro-3-methyl-2-α, β-dibromophenylpropanyol benzofuran (7)

To a solution of benzofuran analogue of chalcone **(2)** (0.01 mol) dissolved in acetic acid (30 mL), a mixture of bromine in acetic acid (2 mL, 10%) was added in portions with shaking. After the complete addition of bromine solution, the resulting mixture was kept at room temperature for 4 h. The reaction mixture was decomposed in ice water and the solid that separated was filtered, washed with sodium thiosulfate solution; then with water and then dried and crystallized from ethanol. Yield 69%, m. p. 170ºC α, β-dibromophenylpropionylbenzofuran chalcones was identified by physical and analytical data.

Similarly the compounds of the series **(8-11)** were prepared (Table 1)

Table 2. Results of antimicrobial activity of compounds 7-16

Compound	Zone of inhibition (in mm)*			
	Antibacterial		Antifungal	
	S. aureus	***E. coli***	***A. niger***	***C. albicans***
(7)	17	16	18	20
(8)	15	16	19	21
(9)	16	16	20	21
(10)	14	17	20	18
(11)	15	16	16	15
(12)	12	13	-	14
(13)	12	9	13	15
(14)	15	14	16	14

Cont…

Compound	Zone of inhibition (in mm)*			
	Antibacterial		Antifungal	
	S. aureus	*E. coli*	*A. niger*	*C. albicans*
(15)	16	15	14	12
(16)	13	10	14	12
Control DMF	8	8	8	8
Standard Ciprofloxacin	20	21	-	-
Gentamycin	-	-	26	25

* Diameter of the well is 8 mm

3-Phenyl-2-(5'-chloro-3'-methylbenzofuran-2'-yl)-1,4-quinoxalyl methanes (12)

A mixture of 5-chloro-3-methyl-2-α,β-dibromophenyl propanoylbenzofuran **(7)** (0.001 mL) and o-phenylenediamine (0.001mol) was dissolved in methanol (10 mL) and a few drops of concentrated sulphuric acid were added. The reaction mixture was heated at 60-70 °C for 30 min. It was then diluted with water and extracted with ether to remove unreacted o-phenylenediamine. The solid obtained after removal of ether was collected and crystallised from ethanol. Yield 80%, m. p. 200ºC. IR (KBr) cm^{-1} 3074(C-H, str.Ar), 2910 (C-H, str, CH_3), 1600 (C=N), 1439,1400, 1369 (C=C, Ar). ^1H NMR ($CDCl_3$) δ ppm 2.5(s, 3H, CH_3), 3.5(s, 2H, CH_2) and 7.2-7.6(m, Ar-H). Mass spectra m/z M^+, M^{+2}), other prominent peaks are 307, 309, 273, 192, 154, 138 and 115.

Similarly other compounds **(13-16)** of the series were prepared (Table 1)

RESULTS AND DISCUSSION

Quinoxalines have been found to possess antibacterial, antifungal, antibiotic and antitumer properties. The benzofuran analogues of chacones **(2-6)** were synthesized by Claisen-Schmidt condensation of 5-chloro-3-methyl-2-acetyl benzofuran **(1)** with appropriate aromatic aldehydes. Various benzofuran analogues of chalcones **(2-6)** upon bromination gave dibromo derivatives of benzofuran analogues of chalcones **(7-11)**. The above titled compounds **(12-16)** were prepared by the reaction of dibromo derivatives of benzofuran analogues of chalcones **(7-11)** with orthophenylenediamine. The purity of all compounds was checked by TLC with suitable solvent. The structure of synthesized compounds were characterized by spectral analysis.

ACKNOWLEDGEMENT

Authors thank Professor and Chairman, Department of Studies and Research in Chemistry, Gulbarga University, Gulbarga and Principal, Karnataka College of Pharmacy, Bidar, for providing facilities and encouragement. Thanks are due to IISc Bangalore and IIT, Chennai for providing IR, ^{1}H NMR and mass spectra.

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Accepted : 22.11.2007