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Synthesis and Biological Evaluations of Some Benzofuran Derivatives

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In the present work, some new benzofuran derivatives *i.e.*, benzofuran-2-carbohydrazide synthesized by ethyl benzofuran-2-caboxylate with various substituated aromatic aldehyde to give Schiff base and obtained compound were cyclized with carbon disulphide and alcoholic potassium hydroxide to obtain various benzofuran derivatives. The structure of the products was characterized by spectral data. All the compounds were evaluated for antibacterial activity against *Staphylococcus aureus* and *Escherichia coli*.

Key Words: Antibacterial activity, Synthesis, Benzofuran derivatives.

INTRODUCTION

Benzofuran are the important group of heterocyclic compound, several derivatives of which have been marked as biologically and pharmacologically active product. The literature survey revealed that, benzofuran also possess different biological activities such as antiinflammatory[1], antimicrobial[2], analgesic[3], antihypertensive[4] activity. These observations stimulated us to synthesize some new benzofuran derivatives for better activities.

EXPERIMENTAL

Melting point of all derivatives was determined by open capillary method and are uncorrected. The IR spectra were recorded with KBr pellets on Shimadzu FT-IR-8400S spectrophotometer. ^{1}H NMR were recorded on Bruker spectrospin-200 NMR spectrophotometer and the mass spectral analysis of the compounds was carried out by using Turbospray mass spectrometer.

Synthesis of ethyl benzofuran-2-carboxylate (III): Salicylaldehyde (20.0 mL, 0.164 mol) and diethyl bromomalonate (40.0 mL, 0.168 mol) in ethyl methyl ketone (40.0 mL, 0.555 mol) was treated with anhydrous potassium carbonate (20.0 g,

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0.869 mol). The reaction mixture was refluxed for 18 h on steam bath. Ethyl methyl ketone was distilled off under reduced pressure and the residue formed was dissolved in 400 mL of water and cooled in an ice-bath. It was acidified with dil H_2SO_4. The product formed was extracted with 25 mL portion of solvent ether twice and the extract was washed with sodium bicarbonate solution. It was dried over calcium chloride. Solvent was removed and the residue ethyl benzofuran-2-carboxylate was dried.

Synthesis of benzofuran-2-carbohydrazide (IV): Ethylbenzofuran-2-carboxylate (17.40 g, 0.1 mol) and hydrazine hydrate 99 % (4.8 mL, 0.1 mol) in methanol (35.0 mL) was refluxed for 8 h. The reaction mixture was concentrated and a solid was formed filtered and recrystallized from methanol. The precipitate obtained is benzofuran-2-carbohydrazide.

Synthesis of Schiff bases (V): In a 100 mL round bottom flask, benzofuran-2-carbohydrazide (2.5 g, 0.01 mol) was treated with different aromatic aldehydes (1.72 g, 0.01 mol) in methanol (35.0 mL) containing a drop of glacial acetic acid as a catalyst was refluxed for 4 h and cooled. Methanol was distilled off under pressure. The solid thus obtained were filtered and recrystallized from toluene.

Synthesis of benzofuran derivatives (VIa-e): Schiff bases in ethanol (12 mL) to this solution potassium hydroxide (0.5 g, 0.008 mol) and carbon disulphide (1.0 mL, 0.013 mol) were added. The mixture was refluxed on steam bath for 10 h. The solution was allowed to cool overnight and then concentrated. The solution was left at room temperature and then dissolved in 150.0 mL ice cold water. The resulting solution was acidified with dil HCl and allowed to stand for 12 h. The solid was filtered, air dried and recrystallized from ethanol.

VIa: IR (KBr,ν_{max}, cm^{-1}): 3510 (O-HAr), 2986 (C-HAr), 2820 (C-H aliphatic), 1657 (C=N *str.*), 1325 (C-N *str.*), 1087 (C-O-C *str.*), 1184 (C=S *str.*). ^{1}H NMR (δ, ppm): 6.73-7.96 (m, 11H, ArH), 3.46 (s, 2H, CH_2).

VIb: IR (KBr, ν_{max}, cm^{-1}): 3058 (C-HAr), 2931, 2838 (C-H aliphatic), 1598 (C=N *str.*), 1282 (C-N *str.*), 1245 (C-OCH_3), 1059 (C=S *str.*), 1144 (C-O-C *str.*). ^{1}H NMR (δ, ppm): 6.74-7.89 (m, 7H, ArH), 3.58 (s, 9H, OCH_3), 3.84 (s, 2H, CH_2).

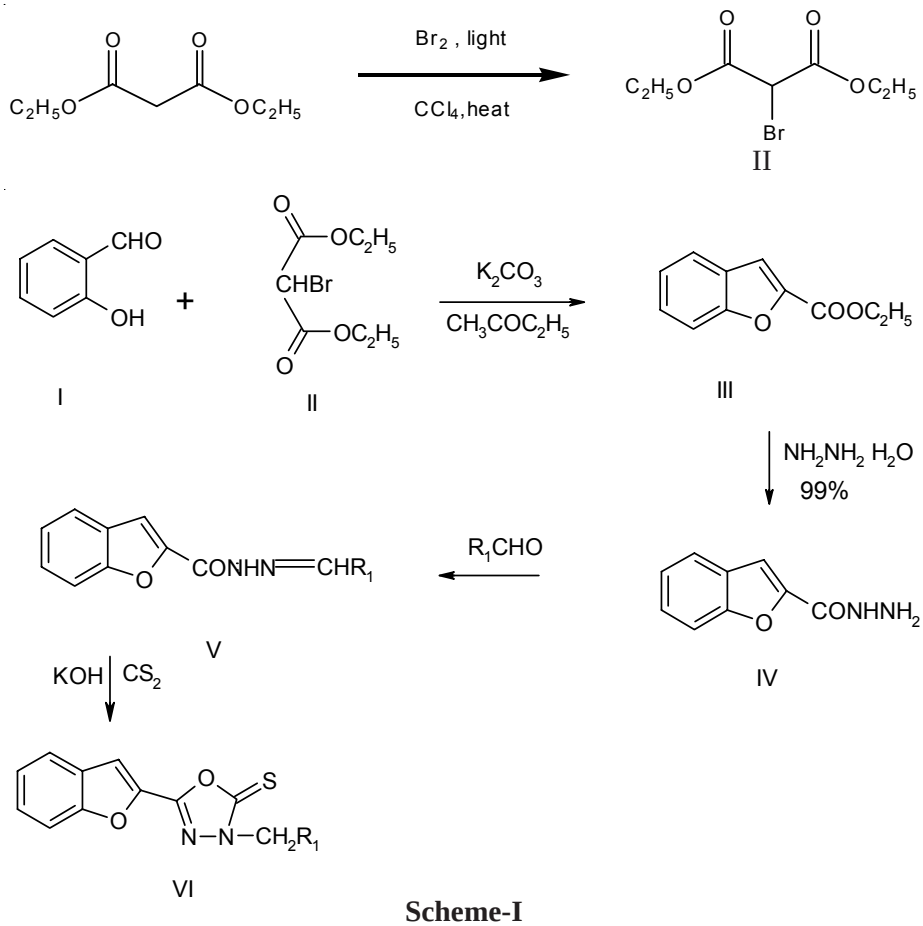
VIc: IR (KBr, ν_{max}, cm^{-1}): 3061 (C-HAr), 2628 (C-H aliphatic), 1603 (C=N *str.*), 1354 (C-N *str.*), 1247 ($COCH_3$), 1090 (C=S *str.*), 1172 (C-O-C *str.*). ^{1}H NMR (δ, ppm): 6.45-8.03 (m, 9H, ArH), 3.16 (s, 3H, OCH_3), 3.90 (s, 2H, CH_2).

VId: IR (KBr,ν_{max}, cm^{-1}): 3466 (O-HAr), 3063 (C-HAr), 2984, 2939 (C-H aliphatic), 1601 (C=N *str.*), 1371 (C-N *str.*), 1097 (C-O-C *str.*), 1182 (C=S *str.*). ^{1}H NMR (δ, ppm): 6.88-7.71 (m, 8H, ArH), 3.38 (s, 2H, CH_2), 4.18 (q, 2H, CH_2), 1.49 (t, 3H, CH_3). Mass spectrum of the compounds exhibited the characteristic signals at: m/z= 369.4.

VIe: IR (KBr, ν_{max}, cm^{-1}): 3059 (C-HAr), 2937, 2816 (CH aliphatic), 1596 (C=N *str.*), 1332 (C-N *str.*), 1202 (C-CH_3), 1059 (C=S *str.*), 1158 (C-O-C *str.*). ^{1}H NMR (δ, ppm): 6.61-7.70 (m, 9H, ArH), 4.30 (s, 2H, CH_2), 8.35 (m, 6H, ArH), 3.94 (s, 3H, OCH_3), 4.30 (s, 2H, CH_2).

TABLE-1
CHARACTERIZATION DATA OF BENZOFURAN DERIVATIVES

Compd.	R_1	m.p. (°C)
VIa	2-Hydroxy-1-naphthaldehyde	197
VIb	3,4,5-Trimethoxy benzaldehyde	190
VIc	2-Methoxy benzaldehyde	142
VId	4-Hydroxy-3-ethoxy benzaldehyde	177
VIe	Pyridine-1-carboxyaldehyde	168



Scheme-I

Antibacterial activity: All the synthesized compounds (**VIa-VIe**) were screened for their antibacterial activity by cup plate diffusion technique[5-8]. The prepared microbial suspension was added in the media and mixed with and transferred into petridish. 16 µg/mL solution of ciprofloxacin and ampicillin 32 µg/mL in DMSO was prepared as standard and 30 µg/mL in DMSO was prepared as sample. The zone of inhibition was measured in millimeter. The result so obtained are recorded in Table-2.

TABLE-2
ANTIBACTERIAL ACTIVITY OF BENZOFURAN DERIVATIVES

Compounds	Zone of inhibition (mm)	
	Staphylococcus aureus	*Escherichia coli*
VIa	10.568±0.1390**	10.163±0.227**
VIb	13.838±0.2780**	11.711±0.242**
VId	9.857±0.2482**	15.865±0.217**
VIe	11.165±0.2340**	11.711±0.242**
Ciprofloxacin (standard 1)	22.168±0.0470**	20.573±0.224**
Ampicillin (standard 2)	11.421±0.1430**	11.108±0.027**
Control	0.037±0.0230**	0.037±0.023**

Values are mean ± SEM, n = 5, **p < 0.01, when compared with control.

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