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Synthesis of N'-(Substituted benzylidene)-1-benzofuran-2-carbohydrazide and 5-(5-Substituted-1-benzofuran-2-yl)-1,3,4-oxadiazole-2-thiol as Potent Antioxidants

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The reactions of substituted benzofuran-2-carbohydrazide (**1**) with various aromatic substituted aldehydes and carbon disulphide yielded corresponding N'-(substituted benzylidene)-1-benzofuran-2-carbohydrazide (**2a-f**) and with CS_2 yielded 5-(5-substituted-1-benzofuran-2-yl)-1,3,4-oxadiazole-2-thiols (**3a-c**), respectively. The synthesized compounds were characterized by IR, ^{1}H NMR and mass spectra. All the compounds were screened for their *in vitro* antioxidant activity using DPPH method and antimicrobial activity by cup-plate diffusion method. The compounds **2c**, **3a** and **3b** shown potent radical scavenging activity and **2a**, **2d**, **3b** and **3c** have shown moderate antimicrobial activity.

Key Words: Synthesis, Substituted benzofuran benzylidine, Benzofuran oxadiazole thiol, Antioxidant and Antimicrobial activities.

INTRODUCTION

In last few years, natural and synthetic benzofuran derivatives have been studied extensively for their chemical and potential biological activities that include antibacterial[1], antiinflammatory[1] and antiasthamatic[2]. In present work, an attempt has been made to synthesize analogues of substituted benzylidene and 1,3,4-oxadiazole-2-thiol containing substituted benzofuran moiety expecting their enhanced antioxidant and antimicrobial activity.

EXPERIMENTAL

All melting points were determined by open capillary tube method using Tempo melting point apparatus and are uncorrected. IR spectra were recorded on a Shimadzu 8400 FTIR spectrophotometer. ^{1}H NMR and mass were analyzed from Indian Institute of Science, Bangalore. The nomenclatures of the synthesized compounds were obtained using ACDFREE10 PC software.

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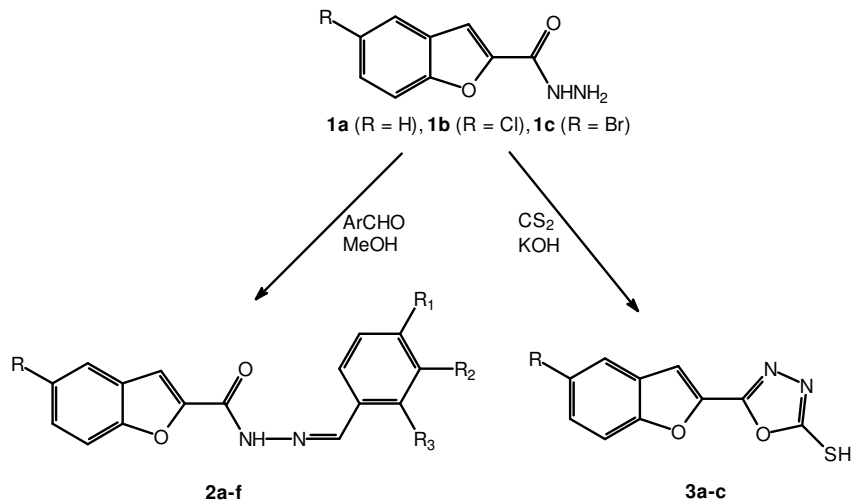
Synthesis of N'-(4-hydroxy-3-methoxybenzylidene)-1-benzofuran-2-carbohydrazide (2a): A mixture of **1a** (0.01 mol) and veratraldehyde (0.01 mol) in methanol containing a drop of glacial acetic acid was refluxed for 4 h and cooled. The solid product obtained was recrystallized from methanol yielded (**2a**). Compounds (**2b-f**) were prepared similarly. Purity of the compound was checked by silica gel plates using *n*-hexane: ethyl acetate (1:4) as mobile phase. **2b-2d** were prepared using **1a** similarly **2e** and **2f** were prepared using **1b** and **1c**, respectively.

Synthesis of 5-(5-bromo-1-benzofuran-2-yl)-1,3,4-oxadiazole-2-thiol (3c): To a solution containing 80 mL of ethanol and potassium hydroxide (0.02 mol, 1.12 g) (dissolved in 4 mL of water) was added to 5-bromo-1-benzofuran-2-carbohydrazide (0.02 mol) (**1c**). After solution occurred, slightly more than one equivalent of carbon disulfide (2.28 g, 2 mL) was added and the mixture was refluxed for 2-3 h or until most of the hydrogen sulfide had been evolved. Occasionally, a solid appeared upon the addition of carbon disulfide, but this usually dissolved on heating. After concentration of the solution to a small volume, the residue was dissolved in water. The precipitate was obtained by adding the solution to ice containing hydrochloric acid. The solid was filtered and dried, recrystallized from alcohol or purified by redissolving in alkali and reprecipitating with acid to yield **3c** (**Scheme-I**). Purity of the compound was checked by silica gel plates using *n*-hexane:ethyl acetate (1:5) as mobile phase.



(**2a**) R=R$_3$=H, R$_1$=R$_2$=OCH$_3$ (**2b**) R=R$_1$=R$_2$=H, R$_3$=OH; (**2c**) R=R$_3$=H, R$_1$=OH, R$_2$=OCH$_3$
(**2d**) R=R$_1$=R$_2$=R$_3$ = H (**2e**) R=Cl, R$_1$=R$_2$=OCH$_3$, R$_3$=H (**2f**) R=Br, R$_1$=R$_2$=OCH$_3$, R$_3$=H
(**3a**) R=H (**3b**) R=Cl (**3c**) R=Br

Scheme-I

RESULTS AND DISCUSSION

Substituted salicylaldehyde and ethylchloroacetate in presence of anhydrous potassium carbonate in dimethylformamide when treated resulted in the simultaneous condensation and cyclization accompanied with partial hydrolysis and decarboxylation giving benzofuran-2-carboxylate which on treatment with hydrazine hydrate gave benzofuran-2-carbohydrazide[3,4] (**1a-c**). Condensation of **1a-c** with substituted aromatic aldehyde yielded corresponding benzylidenes[5-7] (**2a-f**) also 5-(substituted-1-benzofuran-2-yl)-1,3,4-oxadiazole-2-thiol[8] (**3a-c**) were obtained by reaction of (**1a-c**) with carbon disulphide in alcoholic potassium hydroxide. Physical characterization and spectral data are given in Table-1.

TABLE-1
PHYSICAL AND SPECTRAL CHARACTERIZATION DATA

Compd. (m.f.)	Yield (%) / m.p. (ºC)	R_f value	Spectral data
2a ($C_{18}H_{16}N_2O_4$)	80 (200)	0.44	IR (KBr, ν_{max}, cm^{-1}): 3255 (NH), 1670 (C=O), 1591 (C=N). ^{1}H NMR DMSO (d_6) δ: 3.8 (d, 6H, $(OCH_3)_2$), 7-7.8 (m 8H Ar), 8.4 (s, 1H N=CH), 12 (s, 1H, NH), Mass m/z 324. (M^+)
2b ($C_{16}H_{12}N_2O_3$)	78 (195)	0.67	IR (KBr, ν_{max}, cm^{-1}): 3442 (OH), 1633 (C=O), 1587 (C=N). ^{1}H NMR DMSO (d_6) δ: 6.8-8.39 (m, 9H, Ar), 8.3 (s, 1H N=CH), 9.52 (s, 1H OH), 11.9 (s, 1H, NH).
2c ($C_{17}H_{14}N_2O_4$)	75 (238)	0.51	IR (KBr, ν_{max}, cm^{-1}): 3462 (OH), 3232 (NH), 1649 (C=O), 1595 (C=N). ^{1}H NMR DMSO (d_6) δ: 3.8 (s, 3H, OCH_3), 6.8-8.39 (m, 8H, Ar), 8.3 (s, 1H N=CH), 9.52 (s, 1H OH), 11.9 (s, 1H, NH).
2d ($C_{16}H_{12}N_2O_2$)	80 (216)	0.67	IR (KBr, ν_{max}, cm^{-1}): 3200 (NH), 1645 (C=O), 1583 (C=N). ^{1}H NMR $CDCl_3$ δ: 7-7.9 (m, 9H, Ar), 8.3 (s, 1H N=CH), 9.8 (s, 1H, NH)
2e ($C_{18}H_{15}ClN_2O_4$)	72 (193)	0.47	IR (KBr, ν_{max}, cm^{-1}): 3261 (NH), 1664 (C=O), 1566 (C=N), 804 (Ar-Cl). ^{1}H NMR DMSO (d_6) δ: 4 (d, 6H, $(OCH_3)_2$), 6.8-7.9 (m, 7H, Ar), 8.5 (s, 1H N=CH), 12.1 (s, 1H, NH).
2f ($C_{18}H_{15}BrN_2O_4$)	70 (175)	0.48	IR (KBr, ν_{max}, cm^{-1}): 3224 (NH), 1658 (C=O), 1573 (C=N), 802 (Ar-Br). ^{1}H NMR $CDCl_3$ δ: 4 (d, 6H, $(OCH_3)_2$), 6.8-7.9 (m, 7H, Ar), 8.5 (s, 1H N=CH), 12.1 (s, 1H, NH). MS m/z 403.7 (M^{+1})
3a ($C_{10}H_6N_2O_2S$)	75 (235)	0.54	IR (KBr, ν_{max}, cm^{-1}): 1645 (C=N), 3116-2950 (ArH). ^{1}H NMR DMSO (d_6) δ: 6.8-7.9 (m, 4H, Ar), 15 (s, 1H, SH). MS m/z 218
3b ($C_{10}H_5ClN_2O_2S$)	70 (218)	0.4	IR (KBr, ν_{max}, cm^{-1}): 1649 (C=N), 3031-2925 (ArH). 804 (Ar-Cl). ^{1}H NMR $CDCl_3$ δ: 6.8-7.9 (m 4H Ar). MS m/z 252
3c ($C_{10}H_5BrN_2O_2S$)	70 (220)	0.5	IR (KBr, ν_{max}, cm^{-1}): 1627 (C=N), 3082-2927 (ArH), 808 (Ar-Br). ^{1}H NMR DMSO (d_6) δ: 7.4-7.7 (m, 4H, Ar), 15.0 (s, 1H). MS m/z 297

Antioxidant activity: The synthesized compounds (**2a-f** and **3a-c**) were tested for their *in vitro* antioxidant activity by 1,1-diphenyl-2-picryl hydrazyl (DPPH) method. The free radical scavenging potentialities of the compounds were measured in terms of hydrogen donating or radical scavenging ability using methanolic solution of DPPH (1 mL, 0.1 mM) was added to 3 mL of sample solution in methanol at different concentrations (10-40 μg/mL). The test compounds react with DPPH and converts it to 1,1-diphenyl-2-picrylhydrazine. The degree of decolonization indicates the scavenging potentialities of the antioxidant drug. The change in the absorbance produced at 517 nm has been used as a measure of antioxidant activity[9]. Among the compounds tested **2c**, **3a** and **3b** were found to be potent radical scavenging activity than ascorbic acid (Table-2). Scavenging activity was expressed as:

$$\text{DPPH Scavenged (\%)} = \frac{(A_{cont} - A_{test})}{A_{cont}} \times 100$$

TABLE-2
ANTIOXIDANT ACTIVITY OF THE SYNTHESIZED COMPOUNDS (**2a-f**) AND (**3a-c**)

Compd.	Percentage of radical scavenging activity (%)			
	10 μg/mL	20 μg/mL	30 μg/mL	40 μg/mL
2a	1.10	0.90	1.60	1.30
2b	18.20	16.60	17.80	18.60
2c	38.50	51.90	57.30	65.10
2d	13.20	14.30	14.50	15.10
2e	12.10	11.60	12.30	11.60
2f	6.70	8.30	8.80	12.20
3a	35.24	45.03	50.84	91.96
3b	50.60	77.31	79.92	86.27
3c	31.47	46.25	57.38	78.00
Ascorbic acid	30.60	52.30	60.80	70.40

Antimicrobial activity: The synthesized compounds (**2a-f** and **3a-c**) were screened for *in vitro* antimicrobial activity against *S. aureus*, *B. subtilis*, *E. coli* and *S. typhi* was assessed by using cup plate diffusion method. The test solutions were prepared in dimethylsulphoxide (DMSO) alone was carried out, which also works as the control. Streptomycin and ampicillin 50 μg/mL concentrations were used as the standard drug. After 24 h of incubation at 37 ± 1 ºC, zones of inhibition was measured in mm and the activity was compared with standard at same concentrations. Among the compounds tested **2a**, **3b** and **3c** were found to be most potent against *S. aureus, B. subtilis, E. coli* and *S. typhi* (Table-3).

TABLE-3
ANTIMICROBIAL ACTIVITY OF THE SYNTHESIZED COMPOUNDS (**2a-f**) AND (**3a-c**)

Compd.	Antimicrobial activity (50 µg/mL)			
	B. subtilis	*S. aureus*	*E. coli*	*S. typhi*
2a	7	2	3	2
2b	5	3	3	2
2c	4	3	2	3
2d	9	3	2	2
2e	5	2	3	2
2f	3	3	2	2
3a	8	4	3	5
3b	9	6	4	6
3c	6	5	3	5
Ampicillin	20	8	8	18
Streptomycin	11	6	4	8

Zone of inhibition (mm).

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