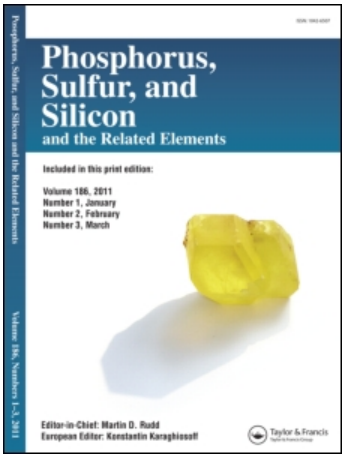

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Synthesis of Triazolyl-Oxadiazolyl-Thiazolyl- and Thiadiazolylbenzofuran of Potential Biological Activity

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SYNTHESIS OF TRIAZOLYL-OXADIAZOLYL-THIAZOLYL- AND THIADIAZOLYLBENZOFURAN OF POTENTIAL BIOLOGICAL ACTIVITY

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*4,7-Dimethoxy (**Ia**) and 4-methoxy (**Ib**) 6-hydroxybenzofuran-5-carbohydrazide were reacted with aryl or alkyl isothiocyanates to give the corresponding thiosemicarbazides (**IIa–h**). Cyclization of the substituted thiosemicarbazides with sodium hydroxide led to the formation of 1,3,4-triazol-2-yl-benzofuran derivatives (**IIIa–d**). Desulfurization of thiosemicarbazide by mercuric oxide gave 1,3,4-oxadiazolyl-benzofuran (**IVa–c**). Treatment of thiosemicarbazide with ethyl bromo-acetate or α-bromopropionic acid yielded 4-thiazolidin-2-yl-carbonyl-benzofuran (**Va–h**). The reaction of compounds **IIb**,**e**,**f** with sulphuric acid or phosphorus oxychloride gave 1,3,4-thiadiazol-2-yl-benzofuran (**VIa–d**, **VII**).*

Keywords: Benzofurans; thiosemicarbazides

INTRODUCTION

A wide variety of pharmacological properties has been shown to be associated with benzofuran derivatives.[1–3] Various thiosemi-carbazides[4] and their cyclized products such as triazoles,[5] oxadiazoles[6,7] thiazolidinones,[8,9] and thiadiazoles are also associated with a broad spectrum of biological properties including analgesic,[6,10] anti-proteolytic,[11] anti inflammatory,[12] muscle relaxant,[7] antifungal, and antibacterial activities.[13]

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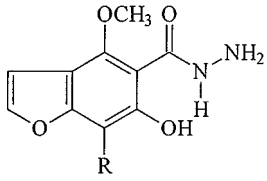
Continuous of our work on the synthesis of heterocyclic compounds derived from the naturally occurring furochromones (khellin and visnagin) of pharmacological interest, This work deals with synthesis and characterization of new compounds containing benzofuran nucleus combined with thiosemicarbazide, 1,3,4-triazolyl, 1,3,4-oxadiazolyl, thiazolidinonyl and 1,3,4-thiadiazolyl moieties which are expected to possess high biological activity.

RESULTS AND DISCUSSION

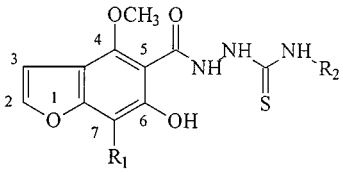
In the present investigation, 4,7-dimethoxy-(**Ia**) and 4-methoxy-6-hydroxybenzofuran-5-carbo-hydrazide (**Ib**) were prepared[14,15] from the naturally occurring khellin and visnagin respectively.



I

a, R = OCH_3; **b,** R = H

Compounds **Ia** and/or **Ib** were reacted with isothiocyanates namely, (benzoyl-, ethyl-, phenyl-, *p*-chlorophenyl-, and cyclohexylisothiocyanate) by heating in dioxane at 80°C for 2 h to afford 1-(4,7-di-methoxy-6-hydroxy-5-benzofuranylcarbonyl)-(**IIa–d**) and 1-(4-methoxy-6-hydroxy-5-benzofuranylcarbonyl)-4-substituted thiosemicarbazides (**IIe–h**) in excellent yields.



II

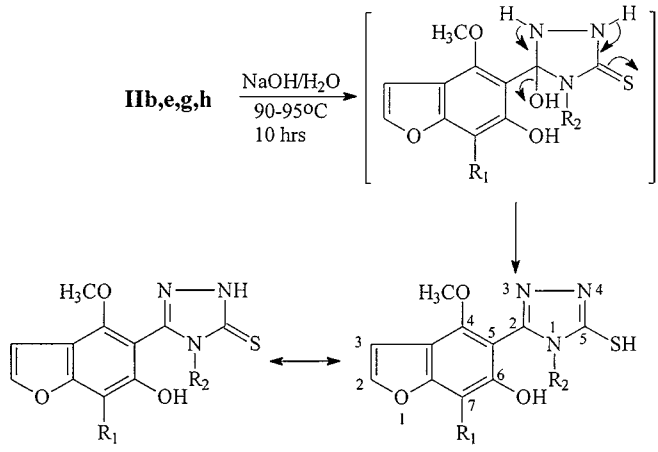
R_1 : a-d = OCH_3 ; e-h = H

R_2: a = COPh; b = CH_2CH_3 ; c = Ph; d = C_6H_4Cl-p; e = CH_2CH_3; f = COPh; g = C_6H_{11}; h = C_6H_4Cl-p

The structures of the products **II** were assigned on the basis of their elemental analysis and spectral data. For example, the infrared spectra

of compounds **II** showed absorption bands at ν 3400–3300 cm^{-1} (OH), 3290–3118 cm^{-1} (NH), 1650–1640 cm^{-1} (C=O) and the vibration coupling due to N–C=S functions at 1240–1280 cm^{-1}.

Cyclization of 1-[4,7-dimethoxy-6-hydroxy-5-benzofuranylcarbonyl)-4-substituted thiosemicarbazide (**IIb**) by heating with sodium hydroxide at 90–95°C for 10 h leads to the formation of 4,7-dimethoxy-6-hydroxy-5-[1-substituted-5-mercapto-1H-1,3,4-triazol-2-yl]benzofuran **IIIa**. Similar treatment of **IIe**,**g**,**h** leads to the formation 4-methoxy-6-hydroxy-5-[1-substituted-5-mercapto-1H-1,3,4-triazol-2-yl]benzofuran **IIIb–d**. (cf. Scheme 1).



III

SCHEME 1

R_1 : a = OCH_3 ; b-d = H

R_2: a,b = CH_2CH_3 ; c = C_6H_{11}; d = C_6H_4Cl-p

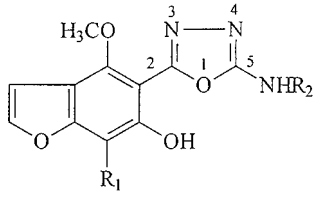
The elemental analysis and spectral data of compounds **IIIa–d** were compatible with the suggested structures. The infrared spectra of compounds **IIIa–d** showed absorption bands at ν 3360–3320 cm^{-1} characteristic for –OH group, 3274–3223 cm^{-1} (NH) and a stretching band in the region of 1614–1625 cm^{-1} characteristic for the C=N of triazole ringe. Meanwhile, the stretching frequency of band C=O was disappeared. In solid state, compounds **IIIa–d** exist predominantly in the thioxo-form as it is shown by the C=S band at 1230–1284 cm^{-1} in the IR spectra of these compounds.[5]

The ^{1}H-NMR spectra of the compounds **III** revealed clearly the absence of two singlet signals corresponding to the two protons of (2NH)

and exhibited two singlets due to OH and SH (exchangeable with D_2O) of triazole.

The observation that several 1,3,4-oxadiazole derivatives exhibit analgesic,[6,7] antiproteolytic,[11] anti-inflammatory,[12] tranquilizing and muscle relaxant[7] properties created an interest in the preparation of the novel series of 4,7-dimethoxy-, (**IVa**,**b**) and 4-methoxy-6-hydroxy-5-(5-substituted amino-1,3,4-oxadiazol-2-yl)benzofuran (**IVc**) for evaluation as antibacterial agents.

Desulfurization of thiosemicarbazides **IIa**,**d**,**h** by yellow mercuric oxide in boiling ethanol yielded 4,7-dimethoxy-, and 4-methoxy-6-hydroxy-5-(5-substituted amino-1,3,4-oxadiazol-2-yl)benzofurans (**IVa–c**) in a good yield.



IV

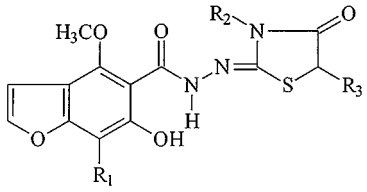
R_1; a,b = OCH_3; c = H

R_2; a = COPh; b,c = C_6H_4Cl-p

The structure of the products **IVa–c** were identified by elemental analysis, IR, ^{1}H-NMR, and mass spectra. The IR spectra of the 1,3,4-oxadiazoles **IVa–c**, lacked the C=O absorption band and showed the OH, NH and C=N vibrational bands.

Various 4-thiazolidinones are associated with a broad spectrum biological properties including anticonvulsant and antibacterial activities.[9,10] Treatment of **IIb**,**d**,**e**,**f**,**g**,**h** with ethyl bromoacetate in the presence of anhydrous sodium acetate, furnished the 4,7-dimethoxy-, (**Va**,**b**) and 4-methoxy-6-hydroxy-5-{[(3-substituted-4-thiazolidinon-2-yl) hydrazino]carbonyl}benzofurans (**Vc–f**). Meanwhile, treatment of compounds **IId**,**h** with α-bromopropionic acid yielded 4,7-dimethoxy-, (**Vg**) and 4-methoxy-6-hydroxy-5-{[(3-p-chlorophenyl-5-methyl-4-thiazolidinon-2-yl)hydrazino]carbonyl}benzo-furan (**Vh**), respectively.

The structure of compounds **Va–f** was confirmed by elemental analysis and spectroscopic methods. For example, the IR spectra of compounds **V** showed C=O bands at 1650-1644 cm^{-1} (CONH–N). The strong band at 1722–1713 cm^{-1} characteristic for C=O of thiazolidinone ring which appeared in the spectra of **V** provided firm support for ring closure.[10,16] The ^{1}H-NMR spectra of compounds **Va–f** revealed clearly



V

R_1; a,b,g = OCH_3; c,-f,h = H

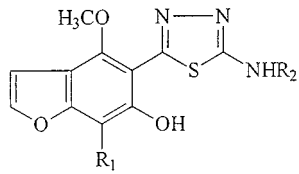
R_2; a,c = CH_2CH_3; b,e,g,h = C_6H_4Cl-p; d = C_6H_{11}; f = COPh

R_3; a-f = H; g,h = CH_3

the absence of the two singlet signals corresponding the two protons of the 2-NH groups. The spectra of compounds **Va–e** displayed an additional singlet at δ 3.90, 4.20, 4.10, 3.85, and 4.05 ppm respectively due to (S—CH_2) which proved thiazolidinone ring closure.[17]

The structures of **Vg** and **Vh** were based on elemental analysis and spectral data.

Furthermore, several 1,3,4-thiadiazole derivatives were reported to possess biological activity. Several procedures were reported for the dehydrative cyclization of substituted thiosemicarbazides to their 1,3,4-thiadiazole analogous utilizing a variety of dehydrating agents, that is, sulphuric acid, phosphorus oxychloride, or polyphosphoric acid. Accordingly, treatment of compounds **IIb**,**e**,**h** with sulphuric acid at ambient temperature for 24 h yielded the corresponding 4,7-dimethoxy- and 4-methoxy-6-hydroxy-5-(5-substituted amino-1,3,4-thiadiazol-2-yl)benzofurans (**VIb–d**) in moderate yields (50–55%). Relatively higher yields (62–66%) of compounds (**VIa–d**) were obtained on carrying out the cyclization by heating of **IIa**,**b**,**e**,**h** with phosphorus oxychloride.



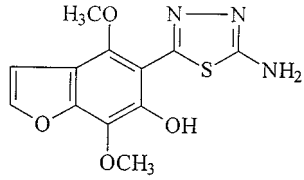
VI

R_1: a,b = OCH_3, c,d = H

R_2: a = COPh; b,c = CH_2CH_3, d = C_6H_4-Cl-p

Attempt to cyclize 1-(4,7-dimethoxy)-6-hydroxy-5-carbonylbenzofuranyl)-4-benzoylthiosemicarbazide (**IIa**) by the action of sulfuric acid failed to yield the target compound **VIa**; the debenzoylated

product 4,7-dimethoxy-6-hydroxy-5-(5-amino-1,3,4-thiadiazole-2-yl)-benzofuran (**VII**) was obtained instead. On the other hand, cyclization of **IIa** using phosphorus oxychloride yielded the target product **VIa**.



VII

The assignment of structures **VIa–d** were based on elemental analysis and spectral data. The IR spectra of **VIa–d** revealed clearly the absence of the stretching band characteristic for O=C–N group and showed the strong bands at ν 1618–1620 cm^{-1} and 3180–3223 cm^{-1} corresponding to C=N and NH groups respectively.

EXPERIMENTAL

All melting points were determined on a GallenKamp electrothermal melting point apparatus and are uncorrected. Elemental analysis was carried out in Microanalytical unit, National Research Centre. Infrared spectra were recorded on Jasco FTIR-300E fourier transform infrared spectrometer and Perkin-elmer FTIR 1000 E spectrum using KBr wafer technique. ^{1}H-NMR spectra were determined on Jeol-EX-270 MHz ^{1}H-NMR spectrometer using TMS as an internal standered. The mass spectra were determined on GC/MS finnigan mat SSQ 7000 Digital DEC 3000. The purity of the synthesized compounds was tested by thin layer chromatography (TLC): Merck Plates.

Preparation of 1-(4,7-dimethoxy-6-hydroxy-5-benzofuranyl-carbonyl)-(IIa–d) and 1-[(4-methoxy-6-hydroxy-5-benzofuranylcarbonyl)-4-substituted Thiosemicarbazides IIa–h

General Procedure

To a suspension of 4,7-dimethoxy-6-hydroxybenzofuran-5-carbohydrazide (**Ia**) and/or 4-methoxy-6-hydroxybenzofuran-5-carbohydrazide (**Ib**) (0.01 mol) in dioxane (50 ml), the appropriate isothiocyanate (0.01 mol) was added. The reaction mixture was heated at 80°C with stirring for 2 h and then left overnight at room temperature. The solid so obtained was filtered and crystallized from the appropriate solvent to give (**IIa–h**) in good yields (see Table I).

TABLE I The Physical and Analytical Data of the New Compounds **IIa–h**

Comp. no.	m.p. °C (yield %)	Appearance solvent of cryst.	Formula (m. wt)	Analysis calcd. found % C	H	N	S
IIa	255	yellow	$C_{19}H_{17}N_3O_6S$	54.93	4.12	10.12	7.72
	(98)	dioxane	(415.44)	54.65	4.06	9.98	7.38
IIb	210	orange	$C_{14}H_{17}N_3O_5S$	49.55	5.05	12.38	9.45
	(90)	ethanol	(339.38)	49.45	5.11	12.35	8.95
IIc	210	colourless	$C_{18}H_{17}N_3O_5S$	55.80	4.42	10.85	8.28
	(85)	ethanol	(387.42)	56.06	4.51	10.59	7.88
IId	245	buff	$C_{18}H_{16}ClN_3O_5S$	51.25	3.82	9.96	6.60
	(96)	dioxane	(421.86)	51.05	3.64	9.66	7.55
IIe	205	yellow	$C_{13}H_{15}N_3O_4S$	50.47	4.89	13.58	10.37
	(88)	ethanol	(309.35)	50.46	4.87	13.38	10.96
IIf	220	pale yellow	$C_{18}H_{15}N_3O_5S$	56.10	3.92	10.90	8.32
	(95)	dioxane	(385.40)	56.02	3.72	10.20	8.22
IIg	210	colorless	$C_{17}H_{21}N_3O_4S$	56.18	5.82	11.62	8.82
	(87)	ethanol	(363.44)	56.01	6.01	11.17	8.46
IIh	205	colorless	$C_{17}H_{14}ClN_3O_4S$	52.11	3.61	10.73	8.19
	(92)	ethanol	(391.84)	51.99	3.51	10.63	8.09
IIIa	215	brown	$C_{14}H_{15}N_3O_4S$	52.33	4.70	13.08	9.98
	(73)	ethanol/H_2O	(321.36)	51.84	4.73	12.78	9.94
IIIb	250	buff	$C_{13}H_{13}N_3O_3S$	53.60	4.50	14.42	11.01
	(75)	ethanol	(291.33)	53.21	4.56	13.81	10.87
IIIc	235	white	$C_{17}H_{19}N_3O_3S$	59.11	5.54	12.17	9.28
	(68)	ethylacetate/ pet. ether (60–80°C)	(345.42)	58.98	5.65	11.89	8.97
IIId	160	white	$C_{17}H_{12}ClN_3O_3S$	54.62	3.24	11.24	8.58
	(70)	ethanol	(373.82)	54.01	3.62	10.85	7.98
IVa	230	pale gray	$C_{19}H_{15}N_3O_6$	59.84	3.96	11.01	
	(65)	ethanol	(381.35)	58.61	3.74	10.43	
IVb	195	buff	$C_{18}H_{14}ClN_3O_5$	55.75	3.64	10.84	
	(66)	ethanol	(387.78)	54.97	3.50	10.76	
IVc	265	buff	$C_{17}H_{12}ClN_3O_4$	57.14	3.38	11.76	
	(68)	ethanol	(357.75)	56.81	3.35	11.12	
Va	235	colorless	$C_{16}H_{17}N_3O_6S$	50.65	4.52	11.08	8.45
	(90)	$CHCl_3$	(379.40)	50.18	4.25	10.41	8.15
Vb	260	colorless	$C_{20}H_{16}ClN_3O_6S$	52.01	3.49	9.09	6.94
	(86)	ethanol	(461.89)	51.98	3.21	9.10	6.76
Vc	225	white	$C_{15}H_{15}N_3O_5S$	51.57	4.33	12.03	9.18
	(90)	chloroform	(349.37)	51.49	4.14	11.94	9.08
Vd	195	white	$C_{19}H_{21}N_3O_5S$	56.56	5.25	10.42	7.95
	(85)	ethanol	(403.46)	55.90	5.42	9.92	7.79
Ve	275	white	$C_{19}H_{14}ClN_3O_5S$	52.84	3.27	9.73	7.49
	(83)	ethanol	(431.86)	52.28	3.24	9.43	7.32
Vf	222	white cotton	$C_{20}H_{15}N_3O_6S$	56.47	3.55	9.88	7.45
	(78)	ethanol	(425.43)	56.19	3.85	9.46	6.25

(Continued on next page)

TABLE I The Physical and Analytical Data of the New Compounds **IIa–h** *(Continued)*

Comp. no.	m.p. °C (yield %)	Appearance solvent of cryst.	Formula (m. wt)	Analysis calcd. found %			
				C	H	N	S
Vg	230	white	$C_{21}H_{18}ClN_3O_6S$	52.99	3.81	8.83	6.74
	(88)	ethanol	(477.50)	52.01	3.98	7.71	6.90
Vh	224	white	$C_{20}H_{16}ClN_3O_5S$	53.87	3.26	9.42	7.19
	(88)	ethanol	(247.50)	54.05	3.59	9.80	7.50
VIa	>260	brown	$C_{19}H_{15}N_3O_5S$	57.42	3.80	10.57	8.07
	(66)	dioxane/ methanol	(397.41)	57.18	3.68	10.93	8.15
VIb	248	brown	$C_{14}H_{15}N_3O_4S$	52.33	4.70	13.08	9.98
	(62)	ethanol	(321.36)	51.98	4.62	12.85	9.76
VIc	260	brown	$C_{13}H_{13}N_3O_3S$	53.59	4.49	14.42	11.10
	(62)	ethanol	(291.33)	53.28	4.35	14.25	10.98
VId	270	yellow	$C_{17}H_{12}ClN_3O_3S$	54.63	3.24	11.24	8.56
	(65)	dioxane	(373.75)	54.28	3.15	11.40	8.39
VII	>260	gray	$C_{12}H_{11}N_3O_4S$	49.15	3.78	14.33	10.91
	(46)	ethanol	292.98	48.89	3.54	14.01	11.01

Preparation of 4,7-dimethoxy-, and 4-methoxy-6-hydroxy-5-[1-substituted-5-mercapto-1H-1,3,4-triazol-2-yl)benzofuran derivatives IIIa–d

General Procedure

A suspension of thiosemicarbazide derivatives **IIb**,**e**,**g**,**h** (0.01 mol) in sodium hydroxide (5 ml, 2 N), was refluxed under stirring for 10 h. The reaction mixture was then cooled and neutralized with dilute hydrochloric acid. The precipitate thus obtained was filtered, washed with water several times, dried, and crystallized from the proper solvent to give **IIIa–d**. (see Table I).

Preparation of 4,7-dimethoxy-and 4-methoxy-6-hydroxy-5-(5-substituted Amino-1,3,4-oxadiazol-2-yl)benzofuran Derivatives IVa–c

General Procedure

A mixture of the thiosemicarbazides **IIa**,**d**,**h** (0.002 mol) and excess yellow mercuric oxide (2 g) in 30 ml ethanol was refluxed for 4–6 h. The reaction mixture was allowed to cool to room temperature (to allow the sedimentation of the black mercuric sulphide), filtered, and mercuric sulphide was washed with ethanol. The filtrate and alcoholic washing were combined, treated with water until a permenant turbidity existed and allowed to stand overnight. The product was separated and crystallized from the proper solvent to give **IVa–c**. in good yields.

TABLE II The Spectral Data of the Compounds **Va–h**

Comp no.	IR (ν, cm^{-1}) KBr	^{1}H-NMR (DMSO-d_6, δ, ppm)	Mass M^+ (m/z, %)
IIa	3420 (OH); 3211, 3175 (NH); 1670 (CO—Ph); 1647 (C=O—NH) and 1245 (C=S)	3.9, 4.2 (6H, 2s, $2OCH_3$); 7.3, 8.05 (2H, dd, Furan H-3, H-2, J = 2.5 Hz); 7.55, 7.95 (5H, m, Ar—H); 12.0, 12.1, 12.4 and 13.65 (4H, 4s, 3NH and one OH, D_2O exchange)	415 (19%)
IIb	3367 (OH); 3274, 3166 (NH); 1643 (CO—NH) and 1284 (C=S)	1.1 (3H, t, $CH_2\underline{CH_3}$); 3.45 (2H, q, $\underline{CH_2}CH_3$); 3.9 and 4.05 (6H, ss, $2OCH_3$); 7.3, 8.05 (2H, dd, Furan H-3, H-2, J = 2.5 Hz); 7.55–7.95 (m, 5H Ar—H); 7.7, 9.6, 10.25 and 10.9 (4H, 4s, 3NH and one OH, D_2O exchange)	339 (33%)
IIc	3322 (OH); 3270-3118 (NH); 1640 (CO—NH) and 1261 (C=S)	3.9, 4.0 (6H, ss, $2OCH_3$); 7.15, 7.95 (2H, dd, furan H-3, H-2, J = 2.5 Hz); 7.2–7.65 (5H, m, Ar—H); 9.3, 10.1, 10.55 and 11.0 (4H, 4s, 3NH and one OH, D_2O exchange)	387 (6.95%)
IId	—	—	421
IIe	3364 (OH); 3291-3160 (NH); 1643 (CO—NH) and 1279 (C=S)	1.15 (3H, t, $CH_2\underline{CH_3}$); 3.5 (2H, q, $\underline{CH_2}CH_3$); 4.1 (3H, s, OCH_3); 6.75 (1H, s, H-7); 7.2, 7.85 (2H, dd, furan H-3, H-2, J = 2.5 Hz); 7.15, 9.6, 10.25 and 11.25 (4H, 4s, 3NH and one OH, D_2O exchange)	309 (58.8)
IIf	3315 (OH); 3215-3164 (NH); 1670 (CO—Ph); 1640 (CO—NH) and 1253 (C=S)	4.35 (3H, s, OCH_3); 6.75 (1H, H-7); 7.25, 8.0 (2H, dd, furan H-3, H-2, J = 2.5 Hz); 7.5–7.9 (5H, m, Ar—H); 11.95, 12.02, 12.45 and 13.55 (4H, 4s, 3NH and OH, D_2O exchange)	385 (34%)
IIg	3363 (OH); 3273, 3157 (NH); 1650 (CO—NH) and 1252 (C=S)	1.15–2.5 (10H, m, cyclohexyl); 4.1 (1H, m, cyclohexyl); 4.33 (3H, s, OCH_3); 6.55 (1H, s, H-7); 6.85, 7.45 (2H, dd, furan H-3, H-2, J = 2.5 Hz); 6.75, 9.0, 11.0, 12.75 (4H, 4s, 3NH and OH, D_2O exchange)	363 (29.4%)
IIh	3360 (OH); 3247–3160 (NH); 1642 (CO—NH) and 1281 (C=S)	4.1 (3H, s, OCH_3); 6.8 (1H, s, H-7); 7.20, 7.85 (2H, dd, furan H-3, H-2, J = 2.5 Hz); 7.45 and 7.65 (4H, dd, AB system Ar—H, $J_{H.H}$ = 8 Hz); 9.45, 10.15, 10.50 and 11.4 (4H, 4s, 3NH and OH, D_2O exchange)	391 (29.4%)

(Continued on next page)

TABLE II The Spectral Data of the Compounds **Va–h** *(Continued)*

Comp no.	IR (ν, cm^{-1}) KBr	^{1}H-NMR (DMSO-d_6, δ, ppm)	Mass M^+ (m/z, %)
IIIa	3360 (OH); 3274 (NH); 1625 (C═N) and 1284 (C═S)	1.0 (3H, t, $CH_2\underline{CH_3}$); 3.6 (2H, q, $\underline{CH_2}CH_3$); 3.85 (3H, s, OCH_3); 3.9 (3H, s, OCH_3); 7.2, 7.9 (2H, dd, furan H-3, H-2, J = 2.5 Hz); 9.75 and 13.75 (2H, 2s, OH and SH, D_2O exchange)	321 (100%)
IIIb	3360 (OH); 3213 (NH); 1614 (C═N) and 1281 (C═S)	1.05 (3H, t, $CH_2\underline{CH_3}$); 3.7 (2H, q, $\underline{CH_2}CH_3$); 4.05 (3H, s, OCH_3); 6.83 (1H, s, H-7); 7.22, 7.85 (2H, dd, furan H-3, H-2, J = 2.5 Hz); 10.33 and 13.75 (2H, 2s, OH and SH, D_2O exchange)	291 (100%)
IIIc	3320 (OH); 3231 (NH); 1624 (C═N) and 1249 (C═S)	0.8–2.35 (10, m, cyclohexyl); 4.12 (1H, m, cyclohexyl); 4.3 (3H, s, OCH_3); 6.9 (1H, s, H-7); 7.0, 7.45 (2H, dd, furan H-3, H-2, J = 2.5 Hz); 9.45 and 13.40 (2H, 2s, OH and SH, D_2O exchange)	345 (100%)
IIId	3323 (OH); 3220 (NH); 1619 (C═N) and 1236 (C═S)	3.09 (3H, s, OCH_3); 6.62 (1H, s, H-7); 7.20 and 7.45 (4H, dd, AB system Ar—H, J = 8 Hz); 7.1, 7.75 (2H, dd, furan H-3, H-2, $J_{H.H}$ = 2.5 Hz); 10.22 and 13.70 (2H, ss, OH and SH, D_2O exchange)	373 (100%)
IVa	3440 (OH); 3230 (NH); 1670 (CO—Ph) and (CO—Ph) and 1620 (C═N)	3.97 (3H, s, OCH_3); 4.05 (3H, s, OCH_3); 7.27, 8.02 (2H, dd, furan H-3, H-2, J = 2.5 Hz); 7.55–8.19 (5H, m, Ar—H); 10.0, 12.00 (2H, ss, NH and OH, D_2O exchange)	381 (69%)
IVb			387 (91%)
IVc	3330 (OH); 3164 (NH) and 1627 (C═N)	4.05 (3H, s, OCH_3); 6.8 (1H, s, H-7); 7.15, 7.80 (2H, dd, furan H-3, H-2, J = 2.5 Hz); 7.36, 7.65 (4H, dd, Ar—H); 10.35 and 10.7 (2H, ss, NH and OH, D_2O exchange)	357 (100%)
Va	3257 (OH); 3143 (NH); 1713 (CO-ring) and 1650 (C═O—N)	1.25 (3H, t, $CH_2\underline{CH_3}$); 3.7 (2H, q, $\underline{CH_2}CH_3$); 3.9 (2H, s, CH_2-ring); 4.06 and 4.2 (6H, ss, $2OCH_3$); 6.81, 7.55 (2H, dd, furan H-3, H-2, J = 2.5 Hz); 10.7 and 13.4 (2H, ss, OH and NH, D_2O exchange)	379 (66%)
Vb	3276 (OH); 3167 (NH); 1722 (CO-ring) and 1644 (C═O—N)	4.05 and 4.10 (6H, ss, $2OCH_3$); 4.2 (2H, s, —CH_2— of ring); 6.85–7.55 (6H, m, H-3, H-2, of furan + 4Ar—H); 10.6 and 13.15 (2H, ss, NH and OH, D_2O exchange)	461 (45%)

TABLE II The Spectral Data of the Compounds **Va–h** *(Continued)*

Comp no.	IR (ν, cm^{-1}) KBr	^{1}H-NMR (DMSO-d_6, δ, ppm)	Mass M^+ (m/z, %)
Vc	3265 (OH); 1718 (CO-ring) and 1644 (C═O─N)	1.17 (3H, t, $CH_2\underline{CH_3}$); 3.7 (2H, q, $\underline{CH_2}CH_3$); 4.1 (2H, s, ─CH_2-ring); 4.20 (3H, s, OCH_3); 6.70 (1H, s, H-7); 7.15, 7.80 (2H, dd, furan H-3, H-2, J = 2.5 Hz); 10.55 and 11.75 (2H, ss, NH and OH, D_2O exchange)	379 (66%)
Vd	3260 (OH); 3164 (NH); 1715 (CO-ring) and 1650 (C═O─N)	1.15–2.5 (10H, m, cyclohexyl); 4.45 (1H, m, cyclohexyl); 3.85 (2H, s, ─CH_2-ring); 4.26 (3H, s, OCH_3); 6.85 (2H, overlaped of d and s, H-3 of furan, $J_{H.H}$ = 2.5 Hz and H-7); 7.45 (1H, d, furan H-2, $J_{H.H}$ = 2.5 Hz); 10.55 and 13.37 (2H, ss, NH and OH, D_2O exchange)	402.94 (100%)
Ve	3247 (OH); 3158 (NH); 1715 (CO-ring) and 1648 (C═O─N)	4.05 (2H,s -CH_2-ring); 4.20 (3H, s, OCH_3); 6.73 (1H, s, H-7); 7.16, 7.82 (2H, dd, furan H-3, H-2, J = 2.5 Hz); 7.45 and 7.64 (4H, dd, Ar─H); and 10.57, 11.57 (2H, ss, NH and OH, D_2O exchange)	433
Vh		1.65 (3H, d, CH_3-ring); 4.15 (3H, s, OCH_3); 4.55 (1H, q, methine proton of ring); 6.70 (1H, s, H-7); 7.14, 7.85 (2H, dd, furan H-3, H-2, J = 2.5 Hz); 7.45–7.60 (4H, dd, Ar─H); and 10.55, 11.65 (2H, ss, NH and OH, D_2O exchange)	
Vg		1.65 (3H, d, CH_3-ring); 4.15 (3H, s, OCH_3); 4.55 (1H, q, methine proton of ring); 6.70 (1H, s, H-7); 7.14, 7.85 (2H, dd, furan H-3, H-2, J = 2.5 Hz); 7.45–7.60 (4H, dd, Ar─H); and 10.55, 11.65 (2H, ss, NH and OH, D_2O exchange)	
VIa	3400 broad (OH); 3180 (NH); 1679 (CO─Ph) and 1625 (C═N)	3.99, 4.23 (6H, ss, $2OCH_3$); 7.30, 7.95 (2H, dd, furan H-3, H-2, J = 2.5 Hz); 12.96 (1H, s, NH, exchanged with D_2O); and at 13.2 (1H, br.s, OH, exchanged with D_2O)	397 (49%)
VIb	3300 broad (OH); 3190 (NH) and 1620 (C═N)	1.5 (3H, t, $CH_2\underline{CH_3}$); 3.4 (2H, q, $\underline{CH_2}CH_3$); 3.85, 4.05 (6H, ss, $2OCH_3$); 7.25, 7.90 (2H, dd, furan H-3, H-2, J = 2.5 Hz); 12.9 (1H, s, NH exchangeable with D_2O) and 13.2 (1H, br.s, OH exchanged by D_2O)	321.1 (100%)

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TABLE II The Spectral Data of the Compounds **Va–h** *(Continued)*

Comp no.	IR (ν, cm^{-1}) KBr	^{1}H-NMR (DMSO-d_6, δ, ppm)	Mass M^+ (m/z, %)
VIc		1.2 (3H, t, $CH_2\underline{CH_3}$); 3.5 (2H, q, $\underline{CH_2}CH_3$); 4.2 (3H, s, OCH_3); 6.85 (1H, s, H-7); 7.25, 7.95 (2H, dd, furan H-3, H-2, J = 2.5 Hz); 8.30 (1H, s, NH, exchanged by D_2O) and 9.73 (1H, br.s, OH exchanged by D_2O)	291 (100%)
VId	3400 broad (OH); 3223 broad (NH) and 1618 (C═O─N)	4.22 (3H, s, OCH_3); 6.9 (1H, s, H-7); 7.20, 7.92 (2H, dd, furan H-3, H-2, J = 2.5 Hz); 7.40 (2H, d, AB system of p─Cl─Ph, $J_{H.H}$ = 8 Hz); 7.66 (2H, d, 2H of p─Cl phenyl, $J_{H.H}$ = 8 Hz); 10.75 and 10.85 (2H, ss, NH and OH, D_2O exchange)	373 (100%)
VII	3300 (OH); 3140 (NH_2) and 1620 (C═N)	3.95 and 4.07 (6H, ss, $2OCH_3$); 7.05 and 7.30 (2H, dd, furan H-3 and H-2, J = 2.5 Hz); 10.85 (1H, S, OH) and 10.95 and 11 (2H, S, NH_2) exchangable with D_2O	293 (85%)

Preparation of 4,7-dimethoxy- and 4-methoxy-6-hydroxy-5-[(3-substituted-4-thiazolidinone-2-yl)-hydrazono]-carbonyl]-benzofuran Derivatives Va–h

General Procedure

A mixture of the appropriate thiosemicarbazide derivative **IIb**,**d**,**e**,**f**,**g**,**h** (0.005 mol) and ethyl bromoacetate (1.66 g, 0.01 mol) or α-bromopropionic acid (1.52 g, 0.01 mol) in absolute ethanol 40 ml in the presence of anhydrous sodium acetate (3.28 g, 0.04 mol) was refluxed for 3 h. The reaction mixture was cooled, diluted with water, and allowed to stand overnight. The solid thus obtained was washed with water, dried and crystallized from the proper solvent to give **Va–f**.

Preparation of 4,7-dimethoxy- (VIa,b) and 4-methoxy-6-hydroxy-5-[(5-substituted-amino-1,3,4-thiadiazo-2-yl)-benzofuran Derivatives VIa–d, VII

General Procedure

Method A. Phosphorus oxychloride (15 ml) was added to the appropriate thiosemicarbazide **IIa**,**b**,**e**,**g**,**h** (0.005 mol) and the mixture was heated under reflux for 2–4 h. The mixture was then evaporated in vacuo and the residue was washed with dilute ammonium hydroxide

solution and water, dried and crystallized from the appropriate solvent to give (**VIa–d**) VII. in 62–66% yields.

Method B. Concentrated sulphuric acid (15 ml) was added dropwise to the appropriate thiosemicarbazide **IIa**,**b**,**e**,**g**,**h** (0.005 mol) and the mixture was stirred at ambient temperature for 24 h. The mixture was then poured onto crushed ice (100 g) and the separated solid was filtered, washed with dilute ammonium hydroxide solution and water, dried, and crystallized from the appropriate solvent to give (**VIa–d**) VII in 50–55% yield. (The yield of method A and purity were relatively higher than those in method B.)

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