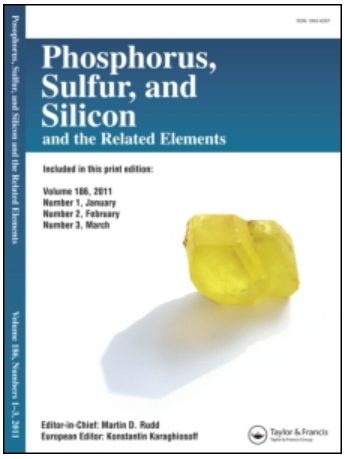

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

SYNTHESIS OF BENZO[1,2-b: 5,4-b']- DIFURANYL-TRIAZOLES, -OXADIAZOLES, -THIAZOLIDINONES, -THIADIAZOLES, AND THE USE OF DNA IN EVALUATION OF THEIR BIOLOGICAL ACTIVITY

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Online publication date: 16 August 2010

To cite this Article Keshk, E. M. , Abu-Hashem, A. A. , Girges, M. M. , Abdel-Rahman, A. H. and Badria, F. A.(2004) 'SYNTHESIS OF BENZO[1,2-b: 5,4-b']- DIFURANYL-TRIAZOLES, -OXADIAZOLES, -THIAZOLIDINONES, -THIADIAZOLES, AND THE USE OF DNA IN EVALUATION OF THEIR BIOLOGICAL ACTIVITY', Phosphorus, Sulfur, and Silicon and the Related Elements, 179: 8, 1577 — 1593
To link to this Article: DOI: 10.1080/10426500490464140
URL: http://dx.doi.org/10.1080/10426500490464140

Phosphorus, Sulfur, and Silicon, 179:1577–1593, 2004

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500490464140

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SYNTHESIS OF BENZO[1,2-b: 5,4-b′]-DIFURANYL-TRIAZOLES, -OXADIAZOLES, -THIAZOLIDINONES, -THIADIAZOLES, AND THE USE OF DNA IN EVALUATION OF THEIR BIOLOGICAL ACTIVITY

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(Received October 15, 2003; accepted December 1, 2003)

Benzo[1,2-b:5,4-b′]difuran-2-carbohydrazides ***5a,b*** *were reacted with aryl or alkyl isothiocyanates to give the corresponding thiosemicarbazides* ***6a–h****. Cyclization of the substituted thiosemicarbazides with sodium hydroxide led to the formation of benzo[1,2-b:5,4-b′]difuranyl-1,3,4-triazoles* ***7a–f****. Desulfurization of thiosemicarbazides by mercuric oxide gave benzo[1,2-b:5,4-b′]difuranyl-1,3,4-oxadiazoles* ***8a–f****. Treatment of thiosemicarbazides with ethyl bromoacetate or α-bromopropionic acid yielded benzo[1,2-b:5,4-b′]difuranyl-carbonyl-hydrazono-4-thiazolidinones* ***9a–f*** *and* ***10a–f****, respectively. Furthermore, the reaction of the thiosemicarbazides with phosphorus oxychloride gave benzo[1,2-b:5,4-b′]difuranyl-1,3,4-thiadiazoles* ***11a–f****. Some compounds in this study were biologically evaluated for their ability to bind to DNA.*

Keywords: Benzodifuran; oxadiazole; thiazole; thiadiazole; triazole

INTRODUCTION

A wide variety of pharmacological properties has been shown to be associated with benzofuran[1–3] and benzodifuran derivatives.[4–6] Various thiosemicarbazides[7,8] and their cyclized products, e.g., triazoles,[9,10] oxadiazoles,[11,12] thiazolidinones,[13,14] and thiadiazoles[15,16] are also associated with a broad spectrum of biological properties.

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In continuation of our research on the synthesis of new heterocyclic compounds derived from the naturally occurring furochromones (visnagin and khellin) of pharmacological interest,[17,18] this work deals with the synthesis and characterization of new compounds containing a benzodifuran nucleus combined with thiosemicarbazide, 1,3,4-triazole, 1,3,4-oxadiazole, thiazolidinone, and 1,3,4-thiadiazole moieties, which are expected to possess high biological activity.

RESULTS AND DISCUSSION

The naturally occurring furochromones (visnagin and khellin) yielded visnaginone **1a** and khellinone **1b** upon hydrolysis with aqueous potassium hydroxide.[19,20] In the present work, both visnaginone **1a** and khellinone **1b** were treated with ethyl bromoacetate in the presence of potassium carbonate to give (4-methoxy- (**2a**) and 4,7-dimethoxy-5-acetylbenzofuran-6-yloxy)acetic acid ethyl ester (**2b**).[21] The ^{1}H NMR spectrum of compound **2a** showed ethyl signals at $\delta = 1.28$ (CH_3), 4.20 (CH_2), and a singlet at $\delta = 4.65$, characteristic for (OCH_2).

Refluxing **2a** or **2b** in dimethylformamide containing anhydrous potassium carbonate afforded 4-methoxy- and 4,8-dimethoxy-3-methylbenzo[1,2-b:5,4-b′]difuran-2-carboxylic acid **3a**,**b**, respectively. Compound **3b** was previously prepared by treatment of khellinone with chloroacetanilide followed by cyclization with 10% NaOH.[21]

The IR spectrum of **3a** revealed an absorption band at 1675 cm^{-1} (C=O). The mass spectrum of **3a** showed a molecular ion peak at m/z = 246.

Treatment of **3a**,**b** with absolute ethanol containing 2–3 drops of concentrated H_2SO_4 gave benzo[1,2-b:5,4-b′]difuran-2-carboxylic acid ethyl esters **4a**,**b**, respectively. The ^{1}H NMR spectra of compounds **4a**,**b** showed ethyl signals at their expected locations. However, refluxing **4a**,**b** with hydrazine hydrate led to the formation of 4-methoxy- and 4,8-dimethoxy-3-methylbenzo[1,2-b:5,4-b′]difuran-2-carbohydrazides **5a**,**b**, respectively. Their infrared (IR) spectra revealed the absence of an ester group and showed absorption band at 1667–1664 cm^{-1} due to the (CONH) group.

Compounds **5a**,**b** were reacted with isothiocyanate derivatives, namely phenyl-, benzyl-, ethyl-, and cyclohexylisothiocyanate, to afford 1-(4-methoxy- and 4,8-dimethoxy-3-methylbenzo[1,2-b:5,4-b′]difuran-2-yl-carbonyl)-4-substituted thiosemicarbazides **6a–h** in excellent yields.

The structures of **6a–h** were assigned on the basis of their elemental analyses and spectral data. IR spectra showed absorption bands

at 3320–3112 cm^{-1} (NH), 1680–1668 cm^{-1} (C=O), and the vibration coupling due to N—C=S functions at 1352–1342 cm^{-1}.

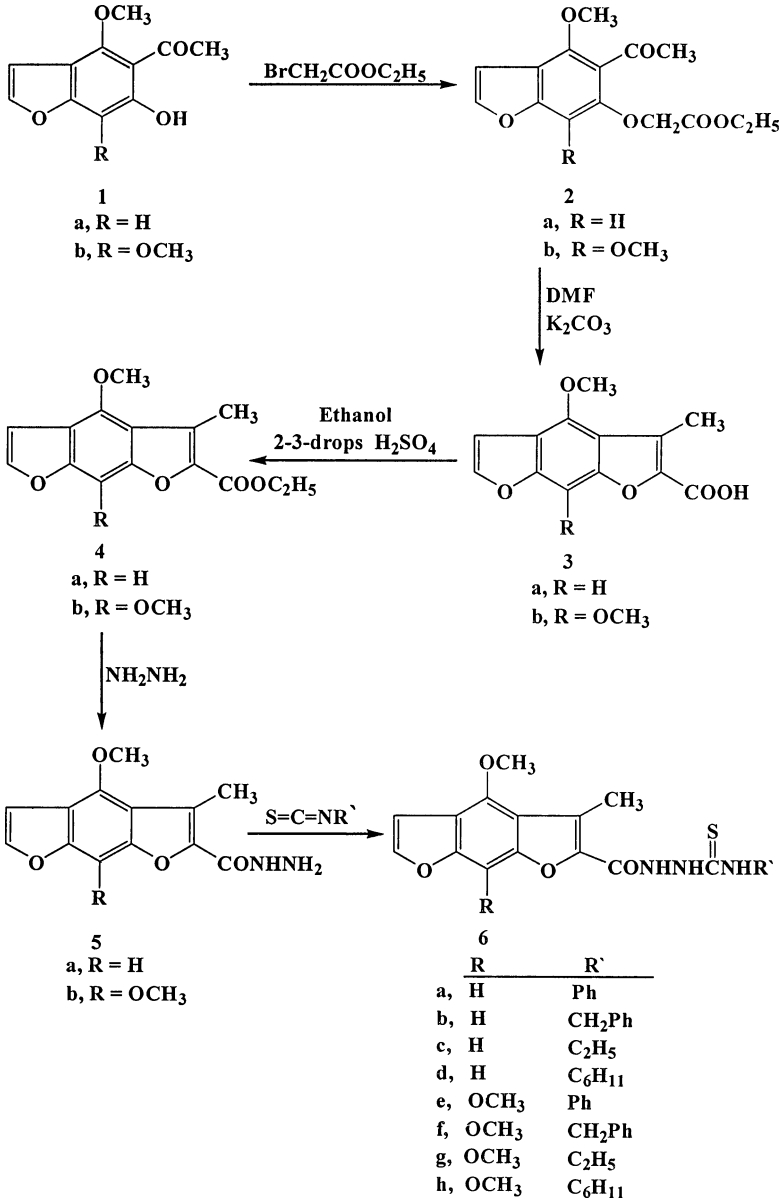
Cyclization of 4-substituted thiosemicarbazides **6a–e,h** by heating with aqueous sodium hydroxide leads to the formation of 2-(4-methoxy- and 4,8-dimethoxy-3-methylbenzo[1,2-b:5,4-b′]difuran-2-yl)-1-substituted-5-mercapto-1H-1,3,4-triazoles 7**a–f**.

The elemental analyses and spectral data of compounds **7a–f** were compatible with the suggested structures. IR spectra showed absorption bands at 3175–3123 cm^{-1} (NH) and a stretching band in the region of 1620–1613 cm^{-1} , characteristic for the C=N of triazole ring. Meanwhile, the stretching frequency of the band C=O disappeared. In the solid states, compounds **7a–f** exist predominantly in the thioxo form, as is shown by the C=S band at 1350–1345 cm^{-1} in the IR spectra of these compounds.[9] The ^{1}H NMR spectra of **7a–f** clearly revealed the absence of two singlet signals corresponding to the two protons of (2 NH) and exhibited one singlet due to SH (exchangeable with D_2O).

Desulfurization of thiosemicarbazides **6a–e,h** by yellow mercuric oxide in boiling ethanol yielded 2-(4-methoxy- and 4,8-dimethoxy-3-methylbenzo [1,2-b:5,4-b′]difuran-2-yl)-5-substituted amino-1,3,4-oxadiazoles **8a–f** in a good yields. Assignment of structures **8a–f** were established on the basis of elemental analyses, IR, ^{1}H NMR, and mass spectra. The IR spectra lacked the C=O absorption band and showed the NH and C=N vibrational bands at 3247–3221 cm^{-1}, and 1621–1613 cm^{-1}, respectively. The mass spectrum of **8a** showed a molecular ion peak at m/z = 361.

Treatment of **6a–e,h** with ethyl bromoacetate furnished 2-{[(4-methoxy- and 4,8-dimethoxy-3-methylbenzo[1,2-b:5,4-b′]difuran-2-yl)-carbonyl]hydrazono}-3-substituted-4-thiazolidinones **9a–f**. The structures of compounds **9a–f** were confirmed by elemental analyses and spectral data. The IR spectra showed the C=O bands at 1660–1650 cm^{-1} (CONH—N) and strong bands at 1725–1713 cm^{-1} characteristic for C=O of thiazolidinone ring, which provided firm support for ring closure. The ^{1}H NMR spectra of **9a–f** revealed clearly the absence of two singlet signals corresponding to the two protons of (2 NH) and displayed an additional singlet signal at $\delta = 3.95$–4.10 ppm due to S—CH_2.

However, treatment of compounds **6a–e,h** with α-bromopropionic acid yielded 2-{[(4-methoxy- and 4,8-dimethoxy-3-methylbenzo[1, 2-b:5,4-b′]difuran-2-yl)carbonyl]hydrazono}-3-substituted-5-methyl-4-thiazolidinones **10a–f**, respectively. The structures of **10a–f** were assigned on the basis of their elemental analyses and spectral data. The ^{1}H NMR spectra of **10a–f** clearly revealed a signal at $\delta = 4.00$–4.10 as a quartet characteristic for the methine proton of thiazolidinone



1
a, R = H
b, R = OCH_3

2
a, R = H
b, R = OCH_3

3
a, R = H
b, R = OCH_3

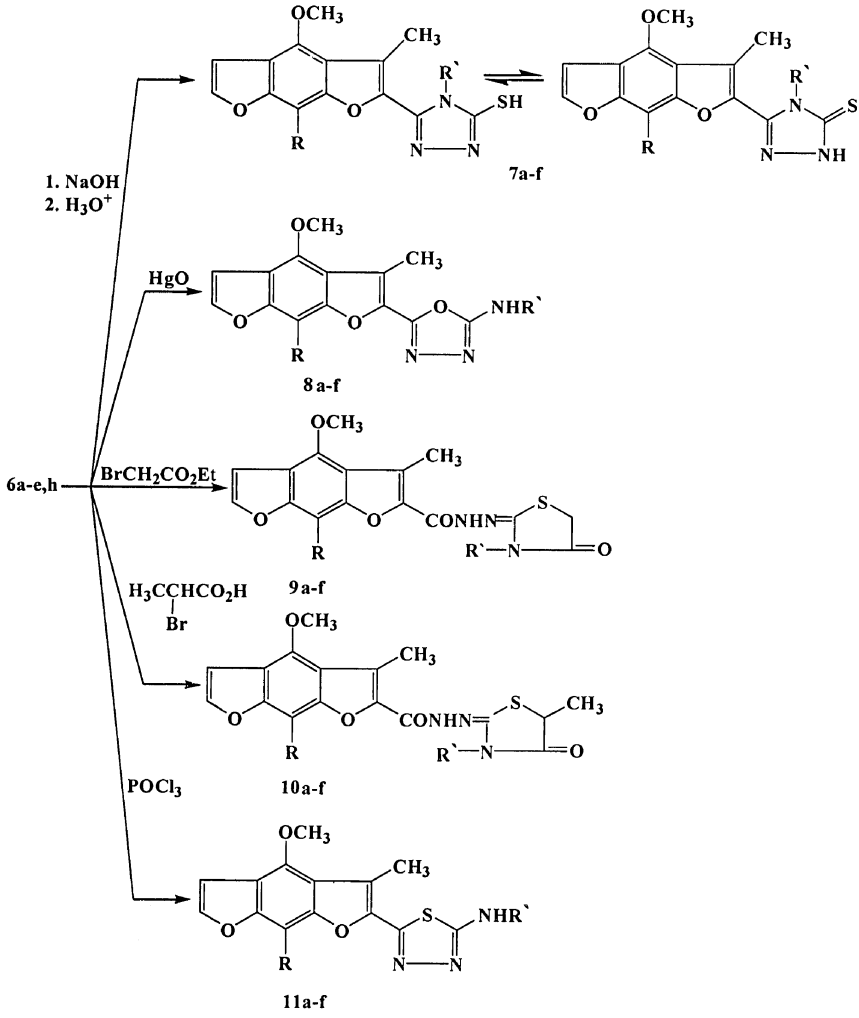
4
a, R = H
b, R = OCH_3

5
a, R = H
b, R = OCH_3

6

	R	R`
a,	H	Ph
b,	H	CH_2Ph
c,	H	C_2H_5
d,	H	C_6H_{11}
e,	OCH_3	Ph
f,	OCH_3	CH_2Ph
g,	OCH_3	C_2H_5
h,	OCH_3	C_6H_{11}

SCHEME 1



	R	R`
a,	H	Ph
b,	H	CH_2Ph
c,	H	C_2H_5
d,	H	C_6H_{11}
e,	OCH_3	Ph
f,	OCH_3	C_6H_{11}

SCHEME 2

ring (H-3), with the disappearance of two singlet signals corresponding to the two protons of 2 NH, which proved thiazolidinone ring closure.

Furthermore, several procedures were reported for the dehydrative cyclization of substituted thiosemicarbazides to their 1,3,4-thiadiazole analogs utilizing a variety of dehydrating agents, e.g., sulphuric acid, phosphorus oxychloride, or polyphosphoric acid. Accordingly, the treatment of compounds **6a–e,h** with phosphorus oxychloride yielded 2-(4-methoxy- and 4,8-dimethoxy-3-methylbenzo[1,2-b:5,4-b′]difuran-2-yl)-5-substituted amino-1,3,4-thiadiazoles **11a–f**. All analytical and spectral data supported the suggested structures.

EXPERIMENTAL

Melting points are uncorrected. Elemental analyses were carried out in the Microanalytical Unit of the Faculty of Science, Cairo University, Egypt. IR spectra were recorded on a Mattson 5000 fourier transform infrared (FTIR) spectrometer. ^{1}H NMR spectra were taken on a Varian-Ex-300 MHz NMR spectrometer using TMS as an internal standard with ($\delta = 0$ ppm). Mass spectra were determined on a GC-MS. QP-1000 (Shimadzu, Japan). The purity of the synthesized compounds was tested by thin layer chromatography (TLC): Merck Plates. The physical and spectral data of the newly compounds are listed in Tables I and II.

(5-Acetyl-4-methoxy-benzofuran-6-yloxy)acetic Acid Ethyl Ester (2a)

A mixture of visnaginone **1a** (0.01 mol), ethyl bromoacetate (0.01 mol), and anhydrous potassium carbonate (0.015 mol) in dry acetone (25 ml) was refluxed for 5 h. The reaction mixture was allowed to cool to room temperature. Water (25 ml) was added, and then the solid that separated was filtered off, dried, and crystallized from pet ether to give **2a**.

4-Methoxy- and 4,8-Dimethoxy-3-methylbenzo-[1,2-b:5,4-b′]difuran-2-carboxylic Acid (3a,b)

A mixture of **2a** or **2b** (0.01 mol) and anhydrous potassium carbonate (0.015 mol) in dimethylformamide (25 ml) was refluxed for 4 h. The reaction mixture was allowed to cool to room temperature. Water (25 ml) was added, and then the solid that separated was filtered off, dried, and crystallized from ethanol to give **3a**,**b**, respectively.

TABLE I The Physical and Aanalytical Data of the Newly Compounds

Compd. no.	m.p.°C (Yield %)	Color solvent of cryst.	Formula (m. wt)	Analysis calcd. found %			
				C	H	N	S
2a	72–74	White	$C_{15}H_{16}O_6$	61.64	5.52		
	(95)	Pet. ether	(292.29)	61.46	5.34		
3a	229–231	Yellow	$C_{13}H_{10}O_5$	63.42	4.10		
	(85)	Ethanol	(246.22)	63.25	4.21		
4a	135–137	Yellow	$C_{15}H_{14}O_5$	65.69	5.14		
	(85)	Ethanol	(274.27)	65.88	5.00		
4b	80–82	Yellow	$C_{16}H_{16}0_6$	63.15	5.30		
	(82)	Acetone	(304.30)	63.00	5.13		
5a	169–171	White	$C_{13}H_{12}N_2O_4$	60.00	4.65	10.76	
	(85)	Acetone	(260.25)	59.85	4.47	10.84	
5b	150–152	White	$C_{14}H_{14}N_2O_5$	57.93	4.86	9.65	
	(80)	Ethanol	(290.27)	57.75	4.67	9.52	
6a	202–204	White	$C_{20}H_{17}N_3O_4S$	60.75	4.33	10.63	8.11
	(92)	Ethanol	(395.43)	60.57	4.15	10.55	8.00
6b	184–186	White	$C_{21}H_{19}N_3O_4S$	61.60	4.68	10.26	7.83
	(90)	Ethanol	(409.46)	61.49	4.49	10.38	7.94
6c	194–196	White	$C_{16}H_{17}N_3O_4S$	55.32	4.93	12.10	9.23
	(88)	Ethanol	(347.39)	55.12	4.74	12.20	9.12
6d	212–214	White	$C_{20}H_{23}N_3O_4S$	59.83	5.77	10.47	7.98
	(85)	Acetone	(401.48)	59.61	5.58	10.40	7.90
6e	198–200	White	$C_{21}H_{19}N_3O_5S$	59.28	4.50	9.88	7.54
	(90)	Ethanol	(425.46)	59.11	4.31	9.97	7.45
6f	209–211	White	$C_{22}H_{21}N_3O_5S$	60.12	4.82	9.56	7.30
	(85)	Acetone	(439.48)	60.29	4.98	9.50	7.22
6g	217–219	White	$C_{17}H_{19}N_3O_5S$	54.10	5.07	11.13	8.50
	(86)	Ethanol	(377.41)	54.25	5.22	11.25	8.42
6h	206–208	White	$C_{21}H_{25}N_3O_5S$	58.45	5.84	9.74	7.43
	(82)	Ethanol	(431.50)	58.28	5.66	9.65	7.35
7a	239–241	Yellow	$C_{20}H_{15}N_3O_3S$	63.65	4.01	11.13	8.49
	(75)	Ethanol	(377.42)	63.47	4.13	11.20	8.40
7b	182–184	White	$C_{21}H_{17}N_3O_3S$	64.44	4.38	10.73	8.19
	(72)	Ethanol	(391.44)	64.27	4.21	10.65	8.30
7c	>250	White	$C_{16}H_{15}N_3O_3S$	58.35	4.59	12.76	9.73
	(70)	Ethanol	(329.37)	58.26	4.41	12.65	9.63
7d	180–182	White	$C_{20}H_{21}N_3O_3S$	62.64	5.52	10.96	8.36
	(68)	Ethanol	(383.46)	62.46	5.34	10.84	8.23
7e	138–140	White	$C_{21}H_{17}N_3O_4S$	61.90	4.20	10.31	7.87
	(70)	Ethanol	(407.44)	61.80	4.35	10.40	7.80
7f	141–143	White	$C_{21}H_{23}N_3O_4S$	61.00	5.61	10.16	7.75
	(66)	Ethanol	(413.49)	61.12	5.48	10.08	7.82
8a	218–220	Yellow	$C_{20}H_{15}N_3O_4$	66.48	4.18	11.63	
	(70)	Ethanol	(361.35)	66.31	4.35	11.70	
8b	139–141	Yellow	$C_{21}H_{17}N_3O_4$	67.20	4.56	11.19	
	(67)	Ethanol	(375.38)	67.34	4.68	11.30	
8c	122–124	Yellow	$C_{16}H_{15}N_3O_4$	61.34	4.82	13.41	
	(65)	Ethanol	(313.31)	61.16	4.64	13.30	

(Continued on next page)

TABLE I The Physical and Aanalytical Data of the Newly Compounds *(Continued)*

Compd. no.	m.p.°C (Yield %)	Color solvent of cryst.	Formula (m. wt)	Analysis calcd. found %			
				C	H	N	S
8d	175–177	Yellow	$C_{20}H_{21}N_3O_4$	65.38	5.76	11.44	
	(65)	Ethanol	(367.40)	65.21	5.62	11.55	
8e	228–230	Yellow	$C_{21}H_{17}N_3O_5$	64.45	4.38	10.74	
	(69)	Methanol	(391.38)	64.29	4.24	10.66	
8f	190–192	Brown	$C_{21}H_{23}N_3O_5$	63.46	5.83	10.57	
	(63)	Acetone	(397.43)	63.32	5.69	10.49	
9a	208–210	White	$C_{22}H_{17}N_3O_5S$	60.68	3.93	9.65	7.36
	(93)	Ethanol	(435.45)	60.51	3.78	9.73	7.45
9b	>250	White	$C_{23}H_{19}N_3O_5S$	61.46	4.26	9.35	7.13
	(90)	Dioxane	(449.48)	61.28	4.39	9.42	7.20
9c	218–220	White	$C_{18}H_{17}N_3O_5S$	55.80	4.42	10.85	8.27
	(88)	Ethanol	(387.41)	55.95	4.55	10.74	8.16
9d	222–224	White	$C_{22}H_{23}N_3O_5S$	59.85	5.25	9.52	7.26
	(85)	Methanol	(441.50)	59.68	5.38	9.60	7.32
9e	178–180	White	$C_{23}H_{19}N_3O_6S$	59.35	4.11	9.03	6.89
	(86)	Ethanol	(465.48)	59.47	4.25	9.10	6.76
9f	181–183	White	$C_{23}H_{25}N_3O_6S$	58.59	5.34	8.91	6.80
	(82)	Acetone	(471.53)	58.41	5.20	9.00	6.72
10a	197–199	White	$C_{23}H_{19}N_3O_5S$	61.46	4.26	9.35	7.13
	(88)	Ethanol	(449.48)	61.29	4.40	9.42	7.20
10b	175–177	White	$C_{24}H_{21}N_3O_5S$	62.19	4.57	9.07	6.92
	(86)	Ethanol	(463.51)	62.33	4.43	9.15	6.85
10c	152–154	White	$C_{19}H_{19}N_3O_5S$	56.85	4.77	10.47	7.99
	(85)	Ethanol	(401.44)	56.66	4.59	10.54	7.87
10d	248–250	White	$C_{23}H_{25}N_3O_5S$	60.64	5.53	9.22	7.04
	(82)	Methanol	(455.53)	60.46	5.38	9.15	7.10
10e	185–187	White	$C_{24}H_{21}N_3O_6S$	60.12	4.41	8.76	6.69
	(85)	Ethanol	(479.51)	60.28	4.57	8.69	6.80
10f	240–242	White	$C_{24}H_{27}N_3O_6S$	59.37	5.60	8.65	6.60
	(80)	Ethanol	(485.55)	59.20	5.42	8.53	6.50
11a	>250	Yellow	$C_{20}H_{15}N_3O_3S$	63.65	4.01	11.13	8.50
	(68)	Dioxane	(377.42)	63.47	4.15	11.20	8.40
11b	145–147	Yellow	$C_{21}H_{17}N_3O_3S$	64.43	4.38	10.73	8.19
	(66)	Acetone	(391.44)	64.25	4.26	10.80	8.25
11c	205–207	Yellow	$C_{16}H_{15}N_3O_3S$	58.35	4.59	12.76	9.73
	(65)	Ethanol	(329.37)	58.48	4.45	12.66	9.63
11d	130–132	Yellow	$C_{20}H_{21}N_3O_3S$	62.64	5.52	10.96	8.36
	(62)	Acetone	(383.46)	62.46	5.38	10.90	8.45
11e	164–166	Yellow	$C_{21}H_{17}N_3O_4S$	61.90	4.21	10.31	7.87
	(67)	Ethanol	(407.44)	61.77	4.32	10.20	7.80
11f	126–128	Yellow	$C_{21}H_{23}N_3O_4S$	61.00	5.61	10.16	7.75
	(60)	Ethanol	(413.49)	61.17	5.47	10.23	7.63

TABLE II The Spectral Data of the Newly Compounds

Comp. no.	IR (ν, cm^{-1}) KBr	^{1}H-NMR ($CDCl_3$, δ, ppm)	MS (m/z)
2a	2928, 2850 (CH-aliph), 1745 (COOEt), 1690 (C═O)	1.28 (t, 3H, $CH_2\underline{CH_3}$), 2.57 (s, 3H, $COCH_3$), 4.07 (s, 3H, OCH_3), 4.20 (q, H, $\underline{CH_2}CH_3$), 4.65 (s, 2H, OCH_2), 6.67 (s, 1H, H-7), 6.87 (d, 1H, $J = 2.30$ Hz, Furan H-3), 7.50 (d, 1H, $J = 2.30$ Hz, Furan H-2)	
3a	2955, 2859 (CH-aliph), 1675 (C═O)	2.39 (s, 3H, CH_3), 4.15 (s, 3H, OCH_3), 6.95 (d, 1H, $J = 2.30$ Hz, Furan H-3), 7.30 (s, 1H, H-8), 7.53 (d, 1H, $J = 2.30$ Hz, Furan H-2)	246
4a	2947, 2852 (CH-aliph), 1708 (COOEt)	1.44 (t, 3H, $CH_2\underline{CH_3}$), 2.77 (s, 3H, CH_3), 4.22 (s, 3H, OCH_3), 4.42 (q, 2H, $\underline{CH_2}CH_3$), 6.99 (d, 1H, $J = 2.30$ Hz Furan H-3), 7.30 (s, 1H, H-8),7.55 (d, 1H, $J =$ 2.30 Furan H-2)	
4b	2945, 2858 (CH-aliph), 1707 (COOEt)	1.42 (t, 3H, $CH_2\underline{CH_3}$), 2.74 (s, 3H, CH_3), 4.07 (s, 3H, OCH_3), 4.24 (s, 3H, OCH_3), 4.40 (q, 2H, $\underline{CH_2}CH_3$) 6.90 (d,1H, $J =$ 2.30 Hz, Furan H-3), 7.52 (d, 1H, $J =$ 2.30 Hz, Furan H-2)	
5a	3324, 3238, 3195 (NH, NH_2), 2949, 2848 (CH-aliph), 1667 (C═O)	2.78 (s, 3H, CH_3), 4.00 (s, 3H, OCH_3), 6.90 (d, 1H, $J = 2.30$ Hz, Furan H-3), 7.28 (s, 1H, 8-H), 7.55 (d, 1H, $J = 2.30$ Hz, Furan H-2), 7.80 (br.s, 2H, NH_2). 9.20 (br.s, 1H, NH)	260
5b	3314, 3225, 3127 (NH, NH_2), 2945, 2849 (CH-aliph), 1664 (C═O)	2.81 (s, 3H, CH_3), 4.06 (s, 3H, OCH_3), 4.26 (s, 3H, OCH_3), 6.92 (d, 1H, $J = 2.30$ Hz, Furan H-3), 7.56 (d, 1H, $J = 2.30$ Hz, Furan H-2), 7.82 (br.s, 2H, NH_2), 9.25 (br. s, 1H, NH)	
6a	3320, 3233, 3149 (NH), 2971, 2851 (CH-aliph), 1679 (C═O), 1352 (C═S)	2.73 (s, 3H, CH_3), 4.10 (s, 3H, OCH_3), 6.90 (d, 1H, $J = 2.30$ Hz, Furan H-3), 7.15–7.40 (m, 6H, 5Ar-H, H-8), 7.55 (d, 1H, $J = 2.30$ Hz Furan H-2), 9.70, 9.86, 10.50 (3br.s, 3H, 3NH)	395
6b	3308, 3252, 3141 (NH), 2978, 2848 (CH-aliph), 1674 (C═O), 1342 (C═S)	2.68 (s, 3H, CH_3), 4.05 (s, 3H, OCH_3), 4.85 (d, 2H, CH_2-Ph), 6.91 (d, 1H, $J = 2.30$ Hz, Furan H-3), 7.20–7.35 (m, 6H, 5 Ar-H, H-8), 7.54 (d,1H, $J = 2.30$ Hz, Furan H-2), 8.70 , 9.15, 10.35 (3br.s, 3H, 3NH)	
6c	3283, 3264, 3148 (NH), 2937, 2865 (CH-aliph), 1673 (C═O), 1343 (C═S)	1.17 (t, 3H, $CH_2\underline{CH_3}$), 2.70 (s, 3H, CH_3), 3.55 (q, 2H, $\underline{CH_2}CH_3$), 4.10 (s, 3H, OCH_3), 6.96 (d, 1H, $J = 2.30$ Hz, Furan H-3), 7.27 (s, 1H, H-8), 7.50 (d, 1H, $J = 2.30$ Hz, Furan H-2), 7.70, 9.50, 10.25 (3br.s, 3H, 3NH)	347

(Continued on next page)

TABLE II The Spectral Data of the Newly Compounds *(Continued)*

Comp. no.	IR (ν, cm^{-1}) KBr	^{1}H-NMR ($CDCl_3$, δ, ppm)	MS (m/z)
6d	3301, 3244, 3142 (NH), 2933, 2854 (CH-aliph), 1675 (C═O), 1348 (C═S)	1.24–1.75 (m, 10H, cyclohexyl), 2.74 (s, 3H, CH_3), 4.12 (m, 1H, cyclohexyl), 4.26 (s, 3H, OCH_3), 6.75 (br.s, 1H, NH), 6.89 (d, 1H, $J = 2.30$ Hz, Furan H-3), 7.35 (s, 1H, 8-H), 7.54 (d, 1H, $J = 2.30$ Hz, Furan H-2), 9.00, 10.52 (2br.s, 2H, 2NH).	401
6e	3290, 3211, 3112 (NH), 3938, 2862 (CH-aliph), 1680 (C═O), 1345 (C═S)	2.74 (s, 3H, CH_3), 4.12 (s, 3H, OCH_3), 4.23 (s, 3H, OCH_3), 6.92 (d, 1H, $J = 2.30$ Hz, Furan H-3), 7.20–7.40 (m, 5H, Ar-H), 7.57 (d, 1H, $J = 2.30$ Hz, Furan H-2), 9.73, 9.90, 10.51 (3br.s, 3H, 3NH).	
6f	3300, 3253, 3163 (NH), 2931, 2850 (CH-aliph), 1668 (C═O), 1344 (C═S)	2.69 (s, 3H, CH_3), 4.06 (s, 3H, OCH_3), 4.22 (s, 3H, OCH_3), 4.86 (d, 2H, CH_2-Ph), 6.90 (d, 1H, $J = 2.30$ Hz, Furan H-3), 7.22–7.35 (m, 5H, Ar-H), 7.50 (d, 1H, $J = 2.30$ Hz, Furan H-2), 8.72, 9.17, 10.40 (3br.s, 3H, 3NH).	439
6g	3297, 3257, 3133 (NH), 2945, 2862 (CH-aliph), 1672 (C═O), 1345 (C═S)	1.20 (t, 3H, $CH_2\underline{CH_3}$), 2.72 (s, 3H, CH_3), 3.56 (q, 2H, $\underline{CH_2}CH_3$), 4.08 (s, 3H, OCH_3) , 4.17(s, 3H, OCH_3), 6.98 (d, 1H, $J = 2.30$ Hz, Furan H-3), 7.56 (d, 1H, $J = 2.30$ Hz, Furan H-2), 7.78, 9.52, 10.28 (3br.s, 3H, 3NH).	
6h	3300, 3242, 3140 (NH), 2934, 2853 (CH-aliph), 1678 (C═O), 1349 (C═S)	1.25–1.80 (m, 10H, cyclohexyl), 2.75 (s, 3H, CH_3), 4.15 (m, 1H, cyclohexyl), 4.25 (s, 3H, OCH_3), 4.42 (s, 3H, OCH_3), 6.70 (br.s, 1H, NH), 6.85 (d, 1H, $J = 2.30$ Hz, Furan H-3), 7.52 (d, 1H, $J = 2.30$ Hz, Furan H-2), 9.16, 10.78 (2br.s, 2H, 2NH)	
7a	3169 (NH), 2942, 2853 (CH-aliph), 1620 (C═N), 1347 (C═S)	2.52 (s, 3H, CH_3), 4.13 (s, 3H, OCH_3), 6.88 (d, 1H, $J = 2.30$ Hz, Furan H-3), 7.16–7.30 (m, 6H, 5Ar-H, H-8), 7.51 (d, 1H, $J = 2.30$ Hz, Furan H-2), 14.20 (s, 1H, SH).	377
7b	3123 (NH), 2930, 2852 (CH-aliph), 1618 (C═N), 1350 (C═S)	2.55 (s, 3H, CH_3), 4.11 (s, 3H, OCH_3), 6.10 (s, 2H, CH_2-Ph), 6.90 (d, 1H, $J = 2.30$ Hz, Furan H-3), 7.15–7.35 (m, 6H, 5Ar-H, H-8), 7.55 (d, 1H, $J = 2.30$ Hz, Furan H-2), 14.00 (br.s, 1H, SH)	
7c	3159 (NH), 2921, 2851 (CH-aliph),1614 (C═N), 1345 (C═S).	0.9 (t, 3H, $CH_2\underline{CH_3}$), 2.53 (s, 3H, CH_3), 4.00 (s, 3H, OCH_3), 4.20 (q, 2H, $\underline{CH_2}CH_3$), 6.98 (d, 1H, $J = 2.30$ Hz, Furan H-3), 7.22 (s, 1H, H-8), 7.58 (d, 1H, $J = 2.30$ Hz, Furan H-2), 14.05 (br.s, 1H, SH)	329
7d	3164 (NH), 2931, 2855 (CH-aliph),1615 (C═N), 1349 (C═S)	1.20–1.90 (m, 10H, cyclohexyl), 2.56 (s, 3H, CH_3), 4.16 (s, 3H, OCH_3), 5.28 (m, 1H, cyclohexyl), 6.95 (d, 1H, $J = 2.30$ Hz, Furan H-3), 7.28 (s, 1H, H-8), 7.55 (d, 1H, $J = 2.30$ Hz, Furan H-2), 14.00 (br.s, 1H, SH)	

TABLE II The Spectral Data of the Newly Compounds *(Continued)*

Comp. no.	IR (ν, cm^{-1}) KBr	^{1}H-NMR ($CDCl_3$, δ, ppm)	MS (m/z)
7e	3175 (NH), 2938, 2847 (CH-aliph),1619 (C═N), 1348 (C═S)	2.52 (s, 3H, CH_3), 4.11 (s, 3H, OCH_3), 4.23 (s, 3H, OCH_3), 6.89 (d, 1H, $J = 2.30$ Hz, Furan H-3), 7.15–7.35 (m, 5H, Ar-H), 7.53 (d,1H, $J = 2.30$ Hz, Furan H-2), 14.15 (br.s, 1H, SH)	407
7f	3166 (NH), 2931, 2854 (CH-aliph), 1613 (C═N), 1347(C═S)	1.24–1.96 (m, 10H, cyclohexyl), 2.50 (s, 3H, CH_3), 4.08 (s, 3H, OCH_3), 4.20 (s, 3H, OCH_3), 5.25 (m, 1H, cyclohexyl), 6.93 (d, 1H, $J = 2.30$ Hz, Furan H-3), 7.32 (s, 1H, H-8), 7.57 (d, 1H, $J = 2.30$ Hz, Furan H-2), 14.08 (br.s, 1H, SH)	
8a	3247 (NH), 2969, 2850 (CH-aliph), 1621 (C═N)	2.70 (s, 3H, CH_3), 3.98 (s, 3H, OCH_3), 6.91 (d, 1H, $J = 2.30$ Hz, Furan H-3), 7.10–7.40 (m, 6H, 5Ar-H, H-8), 7.56 (d, 1H, $J = 2.30$ Hz, Furan H-2), 10.50 (br.s, 1H, NH)	361
8b	3236 (NH), 2931, 2842 (CH-aliph), 1617 (C═N)	2.72 (s, 3H, CH_3), 4.06 (s, 3H, OCH_3), 4.50 (d, 2H, CH_2-Ph), 6.89 (d, 1H, $J = 2.30$ Hz, Furan H-3), 7.12–7.38 (m, 6H, 5Ar-H, H-8), 7.55 (d, 1H, $J = 2.30$ Hz, Furan H-2), 8.50 (br.s, 1H, NH)	
8c	3224 (NH), 2937, 2841 (CH-aliph), 1614 (C═N)	1.30 (t, 3H, $CH_2\underline{CH_3}$), 2.69 (s, 3H, CH_3), 3.55 (q, 2H, $\underline{CH_2}CH_3$), 4.00 (s, 3H, OCH_3), 5.85 (br.s, 1H, NH), 6.90 (d, 1H, $J = 2.30$ Hz, Furan H-3), 7.27 (s, 1H, H-8), 7.57 (d, 1H, $J = 2.30$ Hz, Furan H-2)	313
8d	3221 (NH), 2934, 2850 (CH-aliph), 1612 (C═N)	1.17–1.70 (m, 10H, cyclohexyl), 2.68 (s, 3H, CH_3), 3.79 (m, 1H, cyclohexyl), 4.12 (s, 3H, OCH_3), 4.92 (br.s, 1H, NH), 6.89 (d, 1H, $J = 2.30$ Hz, Furan 3-H), 7.29 (s, 1H, H-8), 7.52 (d, 1H, $J = 2.30$ Hz, Furan H-2)	
8e	3241 (NH), 2970, 2852 (CH-aliph), 1615 (C═N)	2.71 (s, 3H, CH_3), 4.00 (s, 3H, OCH_3), 4.24 (s, 3H, OCH_3), 6.90 (d, 1H, $J = 2.30$ Hz, Furan H-3), 7.12–7.38 (m, 5H, Ar-H), 7.58 (d, 1H, $J = 2.30$ Hz, Furan H-2), 10.60 (br.s, 1H, NH)	391
8f	3230 (NH), 2929, 2854 (CH-aliph),1613 (C═N)	1.20–1.80 (m, 10H, cyclohexyl), 2.66 (s, 3H, CH_3), 3.77 (m, 1H, cyclohexyl), 4.10 (s, 3H, OCH_3), 4.25 (s, 3H, OCH_3), 4.95 (br.s, 1H, NH), 6.91 (d, 1H, $J = 2.30$ Hz, Furan H-3), 7.56 (d, 1H, $J = 2.30$ Hz, Furan H-2)	
9a	3297 (NH), 2947, 2887 (CH-aliph), 1722, 1660 (2C═O), 1618 (C═N)	2.73 (s, 3H, CH_3), 4.09 (s, 2H, CH_2 thiazolidinone ring), 4.13 (s, 3H, OCH_3), 6.93 (d, 1H, $J = 2.30$ Hz, Furan H-3), 7.15–7.40 (m, 6H, 5Ar-H, H-8), 7.6 (d, 1H, $J = 2.30$ Hz, Furan H-2), 10.95 (br.s, 1H, NH)	435

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TABLE II The Spectral Data of the Newly Compounds *(Continued)*

Comp. no.	IR (ν, cm^{-1}) KBr	^{1}H-NMR ($CDCl_3$, δ, ppm)	MS (m/z)
9b	3282 (NH), 2945, 2880 (CH-aliph), 1717, 1657 (2C=O), 1619 (C=N)	2.70 (s, 3H, CH_3), 4.02 (s, 2H, CH_2 thiazolidinone ring), 4.11 (s, 3H, OCH_3), 5.00 (s, 2H, CH_2-Ph), 6.90 (d, 1H, $J = 2.30$ Hz, Furan H-3), 7.12–7.40 (m, 6H, 5Ar-H, H-8), 7.62 (d, 1H, $J = 2.30$ Hz, Furan H-2), 10.35 (br.s, 1H, NH)	
9c	3273 (NH), 2978, 2873 (CH-aliph), 1713, 1650 (2C=O), 1615 (C=N)	1.25 (t, 3H, $CH_2\underline{CH_3}$), 2.71 (s, 3H, CH_3), 3.90 (q, 2H, $\underline{CH_2}CH_3$), 4.00 (s, 2H, CH_2 thiazolidinone ring), 4.17 (s, 3H, OCH_3), 6.96 (d, 1H, $J = 2.30$ Hz, Furan H-3), 7.30 (s, 1H, H-8), 7.65 (d, 1H, $J = 2.30$ Hz, Furan H-2), 10.37 (br.s, 1H, NH)	387
9d	3282 (NH), 2930, 2854(CH-aliph), 1724, 1658 (2C=O), 1613 (C=N)	1.20–1.80 (m, 10H, cyclohexyl), 2.69 (s, 3H, CH_3), 3.95 (s, 2H, CH_2 thiazolidinone ring), 4.15 (s, 3H, OCH_3), 4.25 (m, 1H, cyclohexyl), 7.00 (d, 1H, $J = 2.30$ Hz, Furan H-3), 7.32 (s, 1H, H-8), 7.67 (d, 1H, $J = 2.30$ Hz, Furan H-2), 10.32 (br.s, 1H, NH)	
9e	3295 (NH), 2945, 2883(CH-aliph), 725, 1660 (2C=O), 1616 (C=N)	2.70 (s, 3H, CH_3), 4.10 (s, 2H, CH_2 thiazolidinone ring), 4.16 (s, 3H, OCH_3), 4.27 (s, 3H, OCH_3), 6.98 (d, 1H, $J = 2.30$ Hz, Furan H-3), 7.10–7.35 (m, 5H, Ar-H), 7.62 (d, 1H, $J = 2.30$ Hz, Furan H-2), 11.00 (br.s, 1H, NH)	465
9f	3288 (NH), 2928, 2852(CH-aliph), 1720, 1652 (2C=O), 1610 (C=N)	1.22–1.86 (m, 10H, cyclohexyl), 2.72 (s, 3H, CH_3), 4.00 (s, 2H, CH_2 thiazolodinone ring), 4.13 (s, 3H, OCH_3), 4.27 (m, 1H, cyclohexyl), 4.30 (s, 3H, OCH_3), 7.00 (d, 1H, $J = 2.30$ Hz, Furan H-3), 7.65 (d, 1H, $J = 2.30$ Hz, Furan H-2), 10.42 (br.s, 1H, NH)	
10a	3290 (NH), 2974, 2850 (CH-aliph), 1720, 1659 (2C=O), 1620 (C=N)	1.67 (d, 3H, CH_3), 2.72 (s, 3H, CH_3), 4.07 (q, 1H, methine proton of thiazolidinone ring), 4.11 (s, 3H, OCH_3), 6.93 (d,1H, $J = 2.30$ Hz, Furan H-3), 7.15–7.40 (m, 6H, 5Ar-H, H-8), 7.60 (d, 1H, $J = 2.30$ Hz, Furan H-2), 10.90 (br.s, 1H, NH)	449
10b	3281 (NH), 2985, 2855 (CH-aliph), 1716, 1657 (2C=O), 1619 (C=N)	1.65 (d, 3H, CH_3), 2.70 (s, 3H, CH_3), 4.05 (q, 1H, methine proton of thiazolidinone ring), 4.10 (s, 3H, OCH_3), 5.00 (s, 2H, CH_2-Ph), 6.90 (d, 1H, $J = 2.30$ Hz, Furan H-3), 7.20–7.50 (m, 6H, 5Ar-H, H-8), 7.56 (d, 1H, $J = 2.30$ Hz, Furan H-2), 10.27 (br.s, 1H, NH)	463
10c	3277 (NH), 2979, 2875 (CH-aliph), 1711, 1650 (2C=O), 1614 (C=N)	1.30 (t, 3H, $CH_2\underline{CH_3}$), 1.63 (d, 3H, CH_3), 2.70 (s, 3H, CH_3), 3.95 (q, 2H, $\underline{CH_2}CH_3$), 4.02 (q, 1H, methine proton of thiazolidinone ring), 4.15 (s, 3H, OCH_3), 6.96 (d, 1H, $J = 2.30$ Hz, Furan H-3), 7.30 (s, 1H, H-8), 7.62 (d, 1H, $J = 2.30$ Hz, Furan H-2), 10.32 (br.s, 1H, NH)	401

TABLE II The Spectral Data of the Newly Compounds *(Continued)*

Comp. no.	IR (ν, cm^{-1}) KBr	^{1}H-NMR ($CDCl_3$, δ, ppm)	MS (m/z)
10d	3285 (NH), 2931, 2857 (CH-aliph), 1717, 1654 (2C=O), 1615 (C=N)	1.26–1.88 (m, 10H, cyclohexyl), 1.65 (d, 3H, CH_3), 2.68 (s, 3H, CH_3), 4.00 (q, 1H, methine proton of thiazolidinone ring), 4.15 (s, 3H, OCH_3), 4.26 (m, 1H, cyclohexyl), 7.00 (d, 1H, $J = 2.30$ Hz, Furan H-3), 7.32 (s, 1H, H-8), 7.65 (d, 1H, $J = 2.30$ Hz, Furan H-2), 10.30 (br.s, 1H, NH)	
10e	3287 (NH), 2975, 2852 (CH-aliph), 1722, 1660 (2C=O), 1618 (C=N)	1.69 (d, 3H, CH_3), 2.71 (s, 3H, CH_3), 4.10 (q, 1H, methine proton of thiazolidinone ring), 4.15 (s, 3H, OCH_3), 4.28 (s, 3H, OCH_3), 6.90 (d, 1H, $J = 2.30$ Hz, Furan H-3), 7.10–7.35 (m, 5H, Ar-H), 7.62 (d, 1H, $J = 2.30$ Hz, Furan H-2), 10.92 (br.s, 1H, NH)	479
10f	3280 (NH), 2929, 2855 (CH-aliph), 1718, 1652 (2C=O), 1612 (C=N)	1.20–1.85 (m, 10H, cyclohexyl), 1.65 (d, 3H, CH_3), 2.70 (s, 3H, CH_3), 4.05 (q, 1H, methine proton of thiazolidinone ring), 4.11 (s, 3H, OCH_3), 4.27 (m, 1H, cyclohexyl), 4.30 (s, 3H, OCH_3), 7.00 (d, 1H, $J = 2.30$ Hz, Furan H-3), 7.65 (d, 1H, $J = 2.30$Hz, Furan H-2), 10.40 (br.s, 1H, NH)	
11a	3189 (NH), 2972, 2852 (CH-aliph), 1621 (C=N)	2.68 (s, 3H, CH_3), 4.00 (s, 3H, OCH_3), 6.92 (d, 1H, $J = 2.30$ Hz, Furan H-3), 7.00–7.40 (m, 6H, 5Ar-H, H-8), 7.56 (d, 1H, $J = 2.30$ Hz, Furan H-2), 10.60 (br.s, 1H, NH)	377
11b	3182 (NH), 2930, 2850 (CH-aliph), 1619 (C=N)	2.70 (s, 3H, CH_3), 4.07 (s, 3H, OCH_3), 4.58 (d, 2H, CH_2-Ph), 6.90 (d, 1H, $J = 2.30$, Furan H-3), 7.15–7.40 (m, 6H, 5Ar-H, H-8), 7.57 (d, 1H, $J = 2.30$ Hz, Furan H-2), 8.60 (br.s, 1H, NH)	
11c	3175 (NH), 2928, 2851 (CH-aliph), 1615 (C=N)	1.25 (t, 3H, $CH_2\underline{CH_3}$), 2.69 (s, 3H, CH_3), 3.45(q, 2H, $\underline{CH_2}CH_3$), 4.02 (s, 3H, OCH_3), 6.85 (br.s, 1H, NH), 6.90 (d, 1H, $J = 2.30$ Hz, Furan H-3), 7.29 (s, 1H, H-8), 7.57 (d, 1H, $J = 2.30$ Hz, Furan H-2)	329
11d	3179 (NH), 2933, 2857 (CH-aliph), 1623 (C=N)	1.21–1.90 (m, 10H, cyclohexyl), 2.68 (s, 3H, CH3), 3.44 (m, 1H, cyclohexyl), 4.10 (s, 3H, OCH3), 5.60 (br.s, 1H, NH), 6.90 (d, 1H, $J = 2.30$ Hz, Furan H-3), 7.32 (s, 1H, H-8), 7.54 (d, 1H, $J = 2.30$ Hz, Furan H-2)	
11e	3186 (NH), 2975, 2850 (CH-aliph), 1620 (C=N).	2.71 (s, 3H, CH_3), 4.00 (s, 3H, OCH_3), 4.24 (s, 3H, OCH_3), 6.90 (d, 1H, $J = 2.30$ Hz, Furan H-3), 7.12–7.38 (m, 5H, Ar-H), 7.58 (d, 1H, $J = 2.30$ Hz, Furan H-2), 10.65 (br.s, 1H, NH)	407

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TABLE II The Spectral Data of the Newly Compounds *(Continued)*

Comp. no.	IR (ν, cm^{-1}) KBr	^{1}H-NMR ($CDCl_3$, δ, ppm)	MS (m/z)
11f	3180 (NH), 2932, 2855 (CH-aliph), 1624 (C═N)	1.20–1.92 (m, 10H, cyclohexyl), 2.70 (s, 3H, CH_3), 3.45 (m, 1H, cyclohexyl), 4.12 (s, 3H, OCH_3), 4.25 (s, 3H, OCH_3), 5.62 (br.s, 1H, NH), 6.90 (d, 1H, $J = 2.30$ Hz, Furan H-3), 7.56 (d, 1H, $J = 2.30$ Hz, Furan H-2)	

4-Methoxy- and 4,8-Dimethoxy-3-methylbenzo-[1,2-b: 5,4-b′]difuran-2-carboxylic Acid Ethyl Ester (4a,b)

A mixture of **3a** or **3b** (0.01 mol) in absolute ethanol (25 ml) containing a few drops of concentrated sulphuric acid was refluxed for 2 h. The solid formed was filtered off, dried, and crystallized from the proper solvent to give **4a**,**b**, respectively.

4-Methoxy- and 4,8-Dimethoxy-3-methylbenzo-[1,2-b: 5,4-b′]difuran-2-carbohydrazides (5a,b)

A mixture of **4a** or **4b** (0.01 mol) and hydrazine monohydrate (0.01 mol) in absolute ethanol (25 ml) was refluxed for 2 h and then left to cool. The precipitate formed was filtered off, dried, and crystallized from the proper solvent to give **5a**,**b**, respectively.

1-(4-Methoxy- and 4,8-Dimethoxy-3-methylbenzo-[1,2-b:5,4-b′]difuran-2-yl-carbonyl)-4-substituted Thiosemicarbazides (6a--h)

General Procedure

A mixture of **5a** or **5b** (0.01 mol) and the appropriate isothiocyanate (0.01 mol) in absolute ethanol (25 ml) was refluxed for 2 h and then left to cool. The precipitate formed was filtered off, dried, and crystallized from the appropriate solvent to give **6a–h**.

2-(4-Methoxy- and 4,8-Dimethoxy-3-methylbenzo-[1,2-b: 5,4-b′]difuran-2-yl)-1-substituted-5-mercapto-1H-1,3,4-triazoles (7a--f)

General Procedure

A suspension of appropriate thiosemicarbazides **6a–e,h** (0.01 mol) in sodium hydroxide (50 ml, 2 N) was refluxed under stirring for 4 h. The reaction mixture was then cooled and neutralized with dilute

hydrochloric acid. The precipitate obtained was filtered off, washed with water several times, dried, and crystallized from the proper solvent to give **7a–f**.

2-(4-Methoxy- and 4,8-Dimethoxy-3-methylbenzo-[1,2-b:5,4-b′]difuran-2-yl)-5-substituted Amino-1,3,4-oxadiazoles (8a–f)

General Procedure

A mixture of the appropriate thiosemicarbazides **6a–e,h** (0.01 mol) and excess yellow mercuric oxide (0.015 mol) in ethanol (30 ml) 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), was filtered, and the 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 **8a–f**.

2-{[(4-Methoxy- and 4,8-Dimethoxy-3-methylbenzo-[1,2-b:5,4-b′]difuran-2-yl)carbonyl]hydrazono}-3-substituted-4-thiazolidinones (9a–f)

General Procedure

A mixture of the appropriate thiosemicarbazides **6a–e,h** (0.01 mol), ethyl bromoacetate (0.01 mol), and anhydrous sodium acetate (0.015 mol) in absolute ethanol (30 ml) was refluxed for 3 h. The reaction mixture was cooled, diluted with water, and allowed to stand overnight. The solid obtained was filtered off, dried, and crystallized from the proper solvent to give **9a–f**.

2-{[(4-Methoxy- and 4,8-Dimethoxy-3-methylbenzo-[1,2-b:5,4-b′]difuran-2-yl)carbonyl] hydrazono}-3-substituted-5-methyl-4-thiazolidinones (10a–f)

General Procedure

A mixture of the appropriate thiosemicarbazides **6a–e,h** (0.01 mol), α-bromopropionic acid (0.01 mol), and anhydrous sodium acetate (0.015 mol) in absolute ethanol (30 ml) was refluxed for 3 h. The reaction mixture was cooled, diluted with water, and allowed to stand overnight. The solid obtained was filtered off, dried, and crystallized from the proper solvent to give **10a–f**.

2-(4-Methoxy- and 4,8-Dimethoxy-3-methylbenzo-[1,2-b:5,4-b′]difuran-2-yl)-5-substituted Amino-1,3,4-thiadiazoles (11a–f)

General Procedure

Phosphorus oxychloride (30 ml) was added to the appropriate thiosemicarbazides **6a–e,h** (0.01 mol), and the mixture was refluxed for 2–4 h. The mixture was then evaporated in vacuo, and the residue was washed with dilute ammonium hydroxide solution and water. The solid obtained was filtered off, dried, and crystallized from the proper solvent to give **11a–f**.

DNA-BINDING ASSAY

The mechanism of several known antitumor agents involves interaction with DNA. Examples include alkylating agents (e.g., chlorabucil, cyclophosphamide, melphalan, streptozocin), antitumor, antibiotics (e.g., bleomycin, doxorubicin, mithramycin), and various other substances (e.g., cisplatin, chloroquine). Based on the interaction of small molecular weight with DNA, some short-term procedures have been devised that are applicable for the discovery and evaluation of naturally occurring and synthetic compounds that function by this mechanism.[22–25] Some of the new compounds were screened towards the affinity DNA binding using a colorimetric assay.[26] Compound **7c** showed the highest

TABLE III Activity of Compounds in the Methyl Green/DNA Displacement Assay*

DNA-active compounds	DNA/methyl green IC_{50}, μg/ml
7c	30 ± 3
7a,**b**	49 ± 1
5a	59 ± 1
5b	62 ± 1
8c	65 ± 1
8a,**b**	68 ± 2
11c	72 ± 1
11a,**b**	74 ± 1
2a,**4a**	82 ± 2
2b,**4b**	88 ± 2

*Values represent the concentration (mean ± SD, n = 3 to separate determinations) required for 50% decrease in the initial absorpance of the DNA methyl green solution.

affinity to DNA; compounds **5a**,**b**, **7a**,**b**, **8a–c**, and **11a–c** showed a moderate activity; and the compounds **2a**,**b**, **4a**,**b** showed a weak activity (Table III).

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