Synthesis, characterization and cyclization reactions of some new bisthiosemicarbazones

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Abstract

The reaction of *trans*-1,4-dichloro-2-butene **1** with selected phenols affords (*E*)-1,4-bis(aryloxy)-2-butenes **2a-d** which are converted into bis-thiosemicarbazones **3a-h** *via* the reactions with thiosemicarbazide and 4-methyl thiosemicarbazide, respectively. Similarly, 4-methyl-5-ethoxycarbonyl-2,3-dihydro-1,3-thiazoles **4a-h** are synthesized *via* the reaction of bis-thiosemicarbazones **3a-h** with ethyl 2-chloroacetoacetate. *trans*-1,4-Dithiocyanato-2-butene **5** is obtained from the reaction of KSCN and *trans*-1,4-dichloro-2-butene **1**. Furthermore, the bis-2-amino-1,3,4-thiadiazoles **6k** and **l** are obtained from the reaction of *trans*-1,4-dithiocyanato-2-butene **5** with thiosemicarbazide and 4-methyl thiosemicarbazide, respectively. These compounds are characterized by elemental analyses, infrared, ^{1}H-, ^{13}C-NMR and mass spectrometry. Finally, the microbial features of all compounds are determined. Some of them exhibited microbial activities at low level, and the electronic absorption spectra of the compounds **3b**,**d**,**f** and **h** are measured in organic solvents (MeOH, DMF, DMSO and 1,4-dioxane) with various polarities.

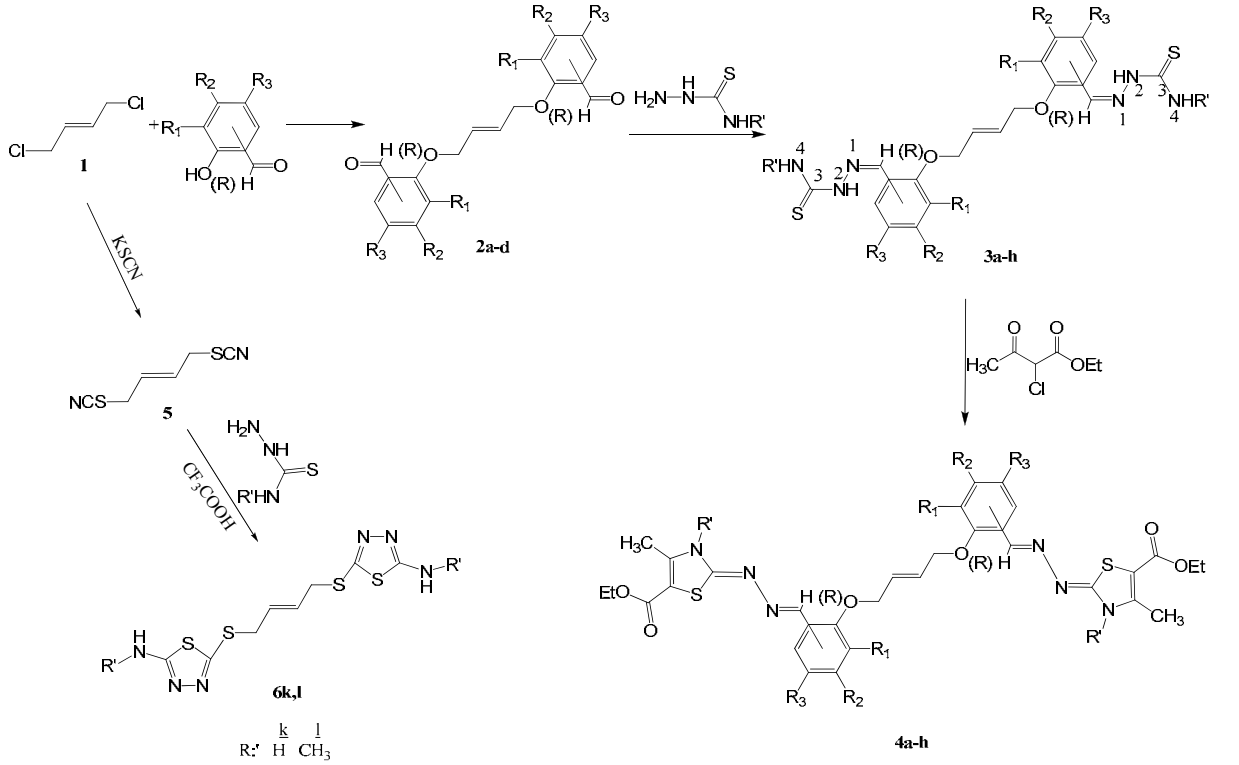
Keywords: Thiosemicarbazone, di-4-methyl-5-ethoxycarbonyl-2,3-dihydro-1,3-thiazole, 2-amino-1,3,4-thiadiazole, Hantzsch reaction

Introduction

Thiosemicarbazones are a class of small molecules that have been evaluated over the last 50 years as antivirals and as anticancer therapeutics, as well as for their parasiticidal action against *Plasmodium falciparum* and *Trypanasoma cruzi* which are the causative agents of malarya and Chagas' disease, respectively.[1-4] In a previous study, the bis(thiosemicarbazone) complexes of copper have shown special promise as radiopharmaceuticals, as illustrated by the per fusion imaging agent.[5-9] Thiosemicarbazones have been reported to exhibit antituberculosis activity.[10,11] In addition, 1,3-thiazoles, 1,3,4-thiadiazoles and their derivatives exhibit various biological

activities such as antituberculosis,[11] antimicrobial,[12] anti-inflammatory,[13] antiviral, anticonvulsant,[14] antihypertensive,[15] local anesthetic,[16] anticancer,[17] hypoglycemic,[18] and cytotoxic activities, among others.[19] 1,3,4-Thiadiazoles and related compounds are of great interest in chemistry owing to their bioactivity of certain plant growth regulating effects as well as antimicrobial activity.[20] Antitubercular activites of thiadiazoles linked with aromatic cycles through the oxy-methylene group have also been reported and compounds of this type have shown inhibition on both cycloxygenase and 5-lipoxygenase activities.[13,21] Lee and coworkers have synthesized some thiadiazoles with antihelmintic activities.[22] More recently, sulfonamide derivatives of 1,3,4-thiadiazoles have been reported to behave as a modulator of anticancer therapies in combination with some cytotoxic compounds.[23,24]

In view of these facts, the aim of the present study was to obtain thiosemicarbazone, 1,3-thiazole and 2-amino-1,3,4-thiadiazole composites (Scheme 1) as possible antitiberculosis, antimicrobial, anti-inflammatory, antiviral, anticonvulsant, antihypertensive, local anesthetic, anticancer, hypoglycemic and cytotoxic agent.



Scheme 1. Synthetic pathway for the preparation of target compounds **2-6**

	a	**b**	**c**	**d**	**e**	**f**	**g**	**h**
R′	H	H	H	H	CH_3	CH_3	CH_3	CH_3

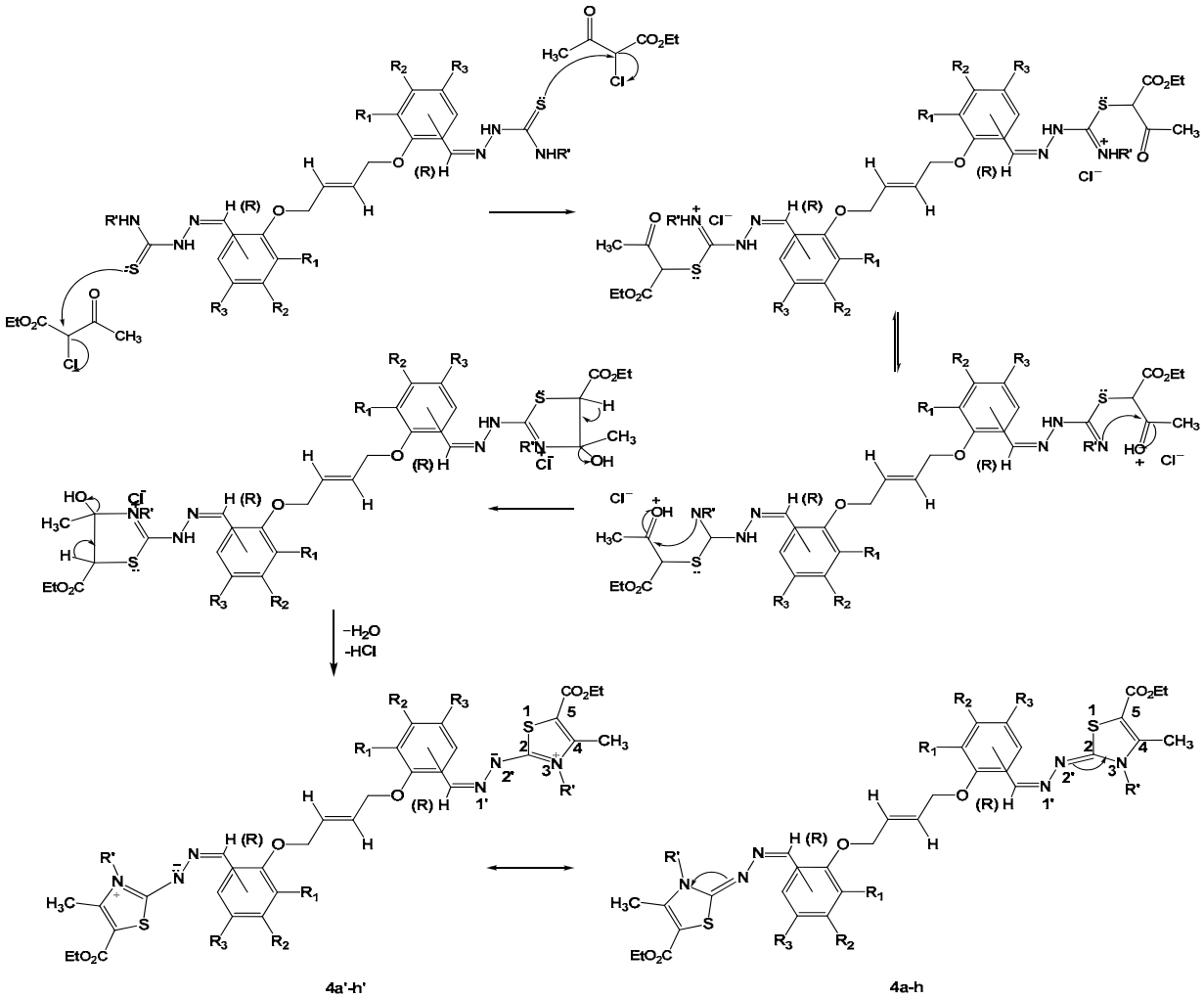
Results and Discussion

In the first part of this study, bis aldehyde and ketone derivatives **2a-d** were obtained from the reaction of *trans*-1,4-dichloro-2-butene **1** with phenolic aldehydes and ketones in absolute ethanol and KOH in reasonable good yields (Scheme 1).

In the IR spectra of compounds **2a-d**, one strong and sharp absorption band was observed at 1681-1668 cm^{-1} belonging to the carbonyl function. The (CHO) Fermi doublet stretching frequency and (C-O-C) stretching frequency were observed at 2875-2756 and 1268-1179 cm^{-1}, respectively. In the ^{1}H-NMR spectra of compounds **2a-d** proton signals belonging to the methylene groups were recorded at 4.98-4.73 ppm (-O-CH_2) integrating for four protons. Aldehyde protons (CHO) were observed at 10.83-9.86 ppm integrating for two protons. In the ^{1}H-NMR spectra of compound **2d**, no signal derived from the ketone function was observed. -HC=CH- proton signals were seen as singlet for compounds **2a-d** at 6.26-6.10 ppm integrating for two protons. In the ^{13}C-NMR the signal of the methylene function of compounds **2a-d**, the OCH_2 group, was observed at 68.71-67.62 ppm. Compounds **2a-d** the signals belonging to C=O and -HC=CH- functional groups appeared at 193.64-188.03 and 128.50-127.78 ppm, respectively.

Bis thiosemicarbazone derivatives **3a-h** were synthesized *via* the reaction of the bis aldehyde and ketone derivatives with thiosemicarbazide and 4-methyl thiosemicarbazide, respectively (Scheme 1). In the IR spectral data of compounds **3a-h**, the ν(C=O) signals 1681-1668 cm^{-1} belonging to the starting aldehydes and ketone starting materials, were absent, while the symmetric and asymmetric stretch bands belonging to the NH_2 group were observed at 3269-3150 cm^{-1}. NH and CH=N stretching frequency were observed at 3155-3140 and 1602-1585 cm^{-1} in the IR spectra, respectively. In the ^{1}H-NMR spectra of compounds **3a-h**, the proton signals appearing for **3a-d** compounds were recorded at 8.37-7.89 ppm (-N*H*$_2$) integrating for four protons (D_2O exchanged) and the proton signals appearing for **3e-h** compounds were recorded 8.66-8.14 ppm (N*H*Me) integrating for two protons (D_2O exchanged). N(2)H protons were observed at 11.67-10.11 ppm integrating for two protons (exchangeable with D_2O) (Scheme 1). In the ^{1}H-NMR spectra of compounds **3a-h**, another characteristic proton signal belonging to CH=N was observed at 8.87-7.97 ppm integrating for two protons. CH=N proton signal for compounds **3d** and **3h** which were ketone thiosemicarbazones were not observed in the ^{1}H-NMR spectra. -HC=CH- proton signals were seen as singlet for compounds **3a-h** at 6.27-6.05 ppm integrating for two protons. The ^{13}C-NMR spectral data of compounds **3a-h**, showed no C=O signal (193.64-188.03 ppm) but indicated the presence of the C=S functionality at 178.43-177.34 ppm in line with reported spectral data.[25-27] The ^{13}C-NMR signals of CH=N function of azomethylene and -HC=CH- function of compounds **3a-h** appeared at 147.63-136.13 and 133.14-128.20 ppm, respectively.

5-Ethoxy-2,3-dihydro-4-methylcarbonyl-1,3-thiazoles **4a-h** were obtained from the Hantzsch reaction between bis-thiosemicarbazones **3a-h** and ethyl 2-chloroacetoacetate (Scheme1). According to this reaction mechanism, the compounds of **4a-d** or **4a'-d'** could be two tautomeric forms while the compounds of **4e-h** or **4e'-h'** are the resonance structures. However, the spectral data and physical parameters show that compounds of **4a-h** have the exo-imine form in 2-position of thiazole group (Scheme 2).



Scheme 2

The most characteristic data for the synthesized compounds **4a-h** was the ν(C=O) IR stretching frequency (1712-1682 cm^{-1}), and the CH=N and C-O-C stretching frequencies were observed at 1611-1590 and 1103-1087 cm^{-1}, respectively. In the ^{1}H-NMR spectra of compounds **4a-d** the characteristic acidic NH proton signal of the thiazole rings (12.41-11.69 ppm) was the most important evidence for the structure of the 1,3-thiazol-2*H*-imine. In the ^{1}H-NMR spectra, the N(2)H proton signal of the thiosemicarbazone was seen at 11.67-10.11 ppm. The spectral data showed that 1,2-dihydro-4-methyl-5-ethoxycarbonyl-1,3-thiazole compounds **4a-h** were obtained and this result was in accordance with the literature.[28] In the D_2O exchange for the compounds, two NH proton signal disappeared in the ^{1}H-NMR spectra. The C-4 methyl protons belonging to thiazoles **4a-h** appeared at 2.57-2.47 ppm while the *N*(3)-methyl proton signals for thiazoles **4e-h** were seen at 3.47-3.42 ppm. The ethyl ester CH_3 protons appeared at 1.39-1.23 ppm and the OCH_2 protons were seen at 4.25-3.83 ppm integrating for four protons. -HC=CH- proton signal was seen as singlet for compounds **4a-h** at 6.22-6.06 ppm integrating for two protons. The ^{13}C-NMR signal of compounds **4a-h** of CH_3 and OCH_2 ester group, the carbons of the thiazole ring CH_3 and -OCH_2- were seen at 68.36-12.52 ppm. This spectral data is the most

evidence for sp^3 hybridized carbons. While C(5) and C(4) of the thiazole ring were observed at 113.48-101.04 and 158.89-146.64 ppm respectively, the exo N(2')=C(2) carbon data of the thiazole ring appeared at 162.73-161.85 ppm in the ^{13}C-NMR spectra. The most characteristic ^{13}C-NMR data was the carbonyl carbon (168.84-165.13 ppm) of the ethyl ester connected to the thiazoles and the absense of the thiosemicarbazones **3a-h** C=S carbon signal (178.43-177.34 ppm).

(*E*)-1,4-Dithiocyanato-2-butene **5** was synthesized using the published methods.[29] Bis 2-amino-1,3,4-thiadiazole derivatives **6** were synthesized via the reaction of (*E*)-1,4-dithiocyanato-2-butene **5** with thiosemicarbazide and 4-methyl thiosemicarbazides, respectively (Scheme 1). In the IR spectral data of compounds **6k** and **l**, symmetric and asymmetric stretching bands belonging to the NH_2 group of the thiadiazole were seen at 3269-3150 cm^{-1}. The C=N stretching frequency was observed at 1640 cm^{-1} in the IR spectra. In the ^{1}H-NMR spectra of compounds **6k** and **l**, the proton signals of N*H*$_2$ and N*H*Me group were recorded at 7.31 ppm and integrated for four protons (D_2O exchanged) and 7.79-7.77 ppm integrating for two protons (D_2O exchanged). *S*-Methylene proton signals were observed at 3.85 and 3.69 ppm integrating for four protons, respectively. A single peak belonging to the -HC=CH- proton signal was seen at 5.76 ppm integrating for two protons. In the ^{13}C-NMR spectra of compounds **6k** and **l**, the sp^3 hybridize S-CH_2 and NH-CH_3 carbons were seen 35.77, 35.38 and 31.11 ppm, respectively. sp^2 Hybridized -HC=CH- carbons were observed at 128.96, 129.37 ppm and sp^2 hybridized carbon peaks, bound to the 2 and 5 position of the thiadiazole ring were seen at 149.24-147.89 and 170.95-169.70 ppm, respectively. The data was consistent with the literature.[20]

Antimicrobial activity

Only a few of the compounds showed mild antimicrobial activity against Gram-positive and Gram-negative bacteria, but none showed antifungal activity against the fungus species (Table 1). These particular bacterial species were tested because they are some of the most common pathogenic and undesirable bacteria frequently involved in food-poisoning incidents. The yeast-like fungus *C. albicans* was included because it is a prevailing and widespread human pathogen. Compounds **3e**, **4a** and **4b** were effective against the Gram-negative bacteria: *E. coli*, *K. pneumoniae* and *P. aeruginosa*, to some extent while compound **4d** was slightly effective against the Gram-negative bacterium *K. pneumoniae*, but not effective against the other two. *K. pneumoniae* seems to be the most vulnerable bacteria against the compounds tested in this study. The compounds **3e** and **6k** are faintly effective against *E. Faecalis* and compound **4h** was the only compound mildly effective against the Gram-positive bacterium *S. aureus*. The tested compounds did not show any activity whatsoever against the Gram-positive spore forming bacterium *B. cereus* and the yeast-like pathogenic fungus *C. albicans.* The reason of lower antimicrobial activity of compounds than we expected might be explained by the low solubility of synthesized compounds.

Table 1. Antimicrobial activities for all compounds

No.	Sol.	Stock Sol. (mg/1 ml)	Test sol. (mg/50 µl)	Microorganisms and inhibition zone (mm)						
				Eco	Kp	Pa	Ef	Sa	Bs	Ca
3a	DMF	10,9	545	-	-	-	-	-	-	-
3b	"	10,2	510	-	-	-	-	-	-	-
3d	"	10,0	500	-	-	-	-	-	-	-
3e	DMSO	10,0	500	+	+	+	+	-	-	-
3f	DMF	10,4	520	-	-	-	-	-	-	-
3g	"	10,0	500	-	-	-	-	-	-	-
3h	"	10,4	520	-	-	-	-	-	-	-
4a	"	10,2	510	+	+	+	-	-	-	-
4b	"	10,0	500	+	+	+	-	-	-	-
4d	"	7,4	370	-	+	-	-	-	-	-
4e	"	13,0	650	-	-	-	-	-	-	-
4f	"	9,8	490	-	-	-	-	-	-	-
4g	"	6,1	310	-	-	-	-	-	-	-
4h	"	10,2	510	-	-	-	-	+	-	-
6k	$CHCl_3$	9,8	490	-	-	-	+	-	-	-
Ceftazidime				+++	+++	+++	+++	+++	+++	
Triflucan										+++

Diameter (mm) of Inhibition Zone: < 5.0: (-); 5.5-10: (+); 11-16: (++); 17-24: (+++)

Abbreviations: Ec: *Escherichia coli* ATCC 35218, Pa: *Pseudomonas aeruginosa* ATCC 10145, Kp: *Klebsiella pneumoniae* ATCC 13883, Ef: *Enterococcus faecalis* ATCC 29212, Sa: *Staphylococcus aureus* ATCC 25923, Bs: *Bacillus cereus* 709 Roma, Ca: *Candida albicans* ATCC 60193.

Solvent and pH effects on the electronic spectra of compounds 3b,d,f and h

The electronic absorption spectra of the compounds **3b**,**d**,**f** and **h** were studied in organic solvents having various polarities, MeOH, DMF, DMSO and 1,4-dioxane. It can be seen from *Tables 2* and *3* that the absorption spectra of all compounds, **3b**,**d**,**f** and **h**, are considerably influenced by changing the solvent. The bands appearing at *ca.* 314-331 nm in dioxane and 302-328 nm in MeOH for all compounds **3b**,**d**,**f** and **h** are shifted to a higher wavelength in DMF and DMSO. The highest red shift is observed in DMSO. The compound has more red shift in DMF and DMSO than other solvents (Figure 1,3,5 and 7). This phenomenon can be explained by the high proton accepting character and the low ionization potential of these solvents.[26,27] As can be seen from Table 2, the UV-vis transitions of related compounds except 1,4-Dioxane were observed as the Bathochromic shift, a change in solvent polarity resulted in solvatochromism. This can be explained by increasing the solvent polarities [$E_T(30)$] values.

Table 2. Electronic spectral data (nm) of all substituted-thiosemicarbazones **3b**,**d**,**f** and **h**

Compd.	1,4-Dioxane [E_T(30) 36.10]	MeOH [E_T(30) 32.66]	DMF [E_T(30) 36.71]	DMSO [E_T(30) 46.45]
3b	254, 283, 295, 314	258, 274, 328	250, 280, 296, 336	273, 300, 302, 353
3d	242, 254, 280, 293, 327	261, 276, 320	245, 260, 303, 317, 335	247, 264, 289, 305, 337
3f	2260, 281, 293, 324, 330	262, 293, 323	268, 289, 291, 335, 348	265, 286, 292, 332, 356
3h	250, 269, 308, 331	279, 302	245, 265, 299, 332	259, 270, 306, 339

The effect of the pH change on the electronic absorption spectra of all compounds were studied in MeOH solution by adding a small amount of 0.1 M HCl and KOH. The λ_{max} of **3b**,**d**,**f** and **h** in methanolic solution is not affected by adding a small amount of 0.1 M KOH. The bands at *ca*. 258-293 nm in neutral MeOH solution of all compounds **3b**,**d**,**f** and **h** are shifted slightly to a higher wavelength in MeOH+KOH solution. On the other hand, the electronic absorption spectra of **3b**,**d**,**f** and **h** show a considerable bathochromic effect when adding a small amount of 0.1 M HCl in methanolic solution. After adding two drops of 0.1 M HCl to methanolic solution of these compounds, the bands appearing at *ca.* 258 and 293 nm in neutral solution show a slight blue shift and in addition, the band at *ca.* 302-328 nm in neutral solution of all compounds is shifted slightly to red visible region (Figure 2,4,6 and 8). Furthermore, a new broad band appears at *ca.* 294-335 nm, indicating that all compounds exist in the –NH.HCl form in acidic solution probably due to the capability of accepting a proton of the secondary amino group. [26,27]

Table 3. Electronic spectral data (nm) of all substituted-thiosemicarbazones (**3b**,**d**,**f** and **h**) in MeOH + HCl and in MeOH + KOH

Compounds	MeOH + HCl	MeOH + KOH
3b	255, 270, 294, 331	250, 278, 330
3d	259, 272, 312, 329	260, 273, 328
3f	260, 291, 310, 335	263, 304, 330
3h	277, 306, 329	276, 306

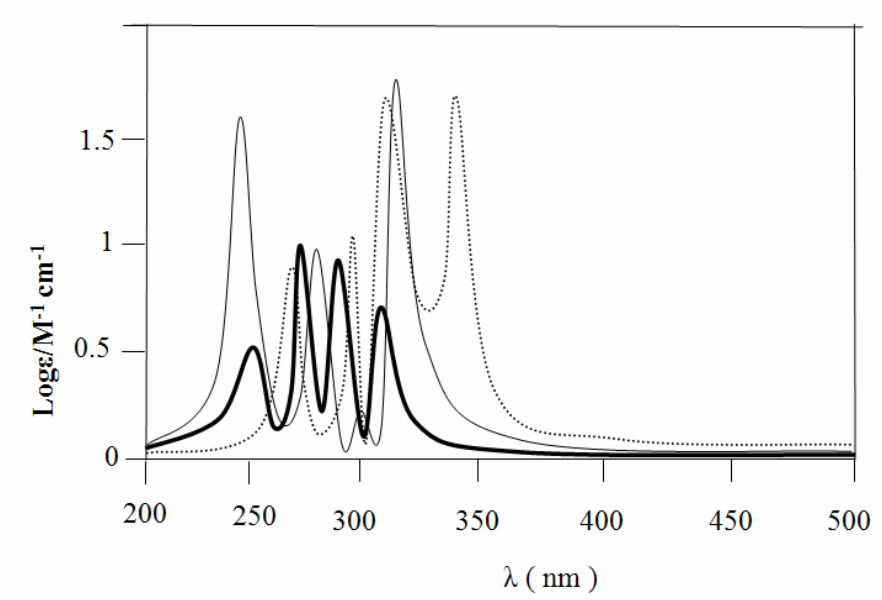


Figure 1. The electronic absorption spectra of Ligand **3b** in: 1,4-Dioxane (bold-black line), DMF (thin-black line) and DMSO (striped-black line).

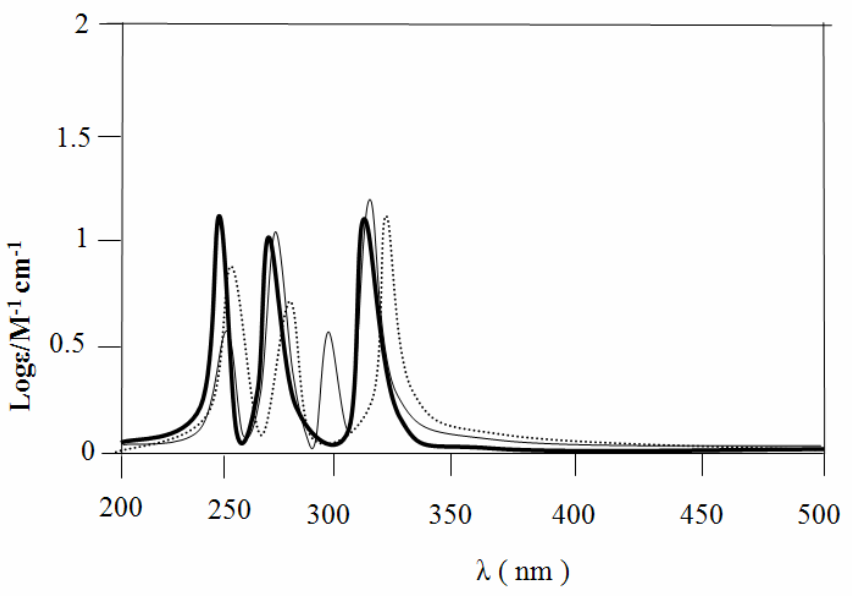


Figure 2. The electronic absorption spectra of Ligand **3b** in: MeOH (striped-black line), MeOH+KOH (bold-black line) and MeOH+HCl (thin-black line).

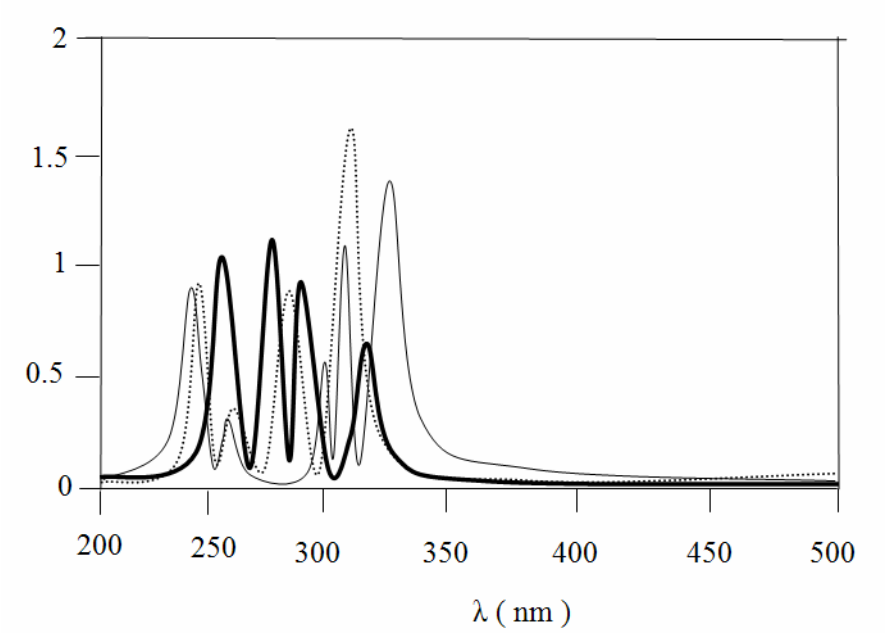


Figure 3. The electronic absorption spectra of Ligand **3d** in: 1,4-Dioxane (bold-black line), DMF (thin-black line) and DMSO (striped-black line).

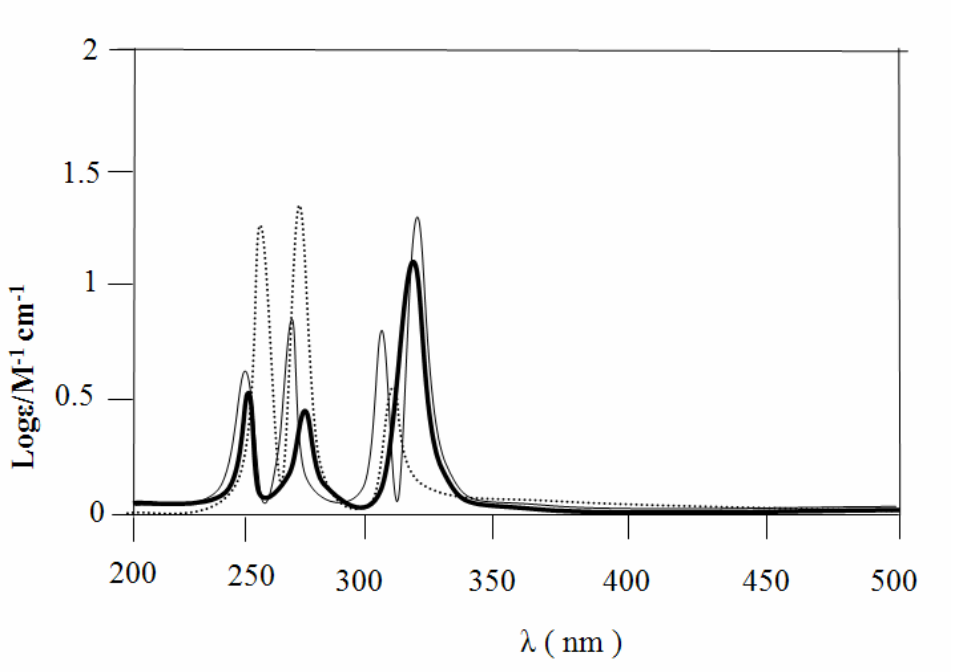


Figure 4. The electronic absorption spectra of Ligand **3d** in: MeOH (striped-black line), MeOH+KOH (bold-black line) and MeOH+HCl (thin-black line).

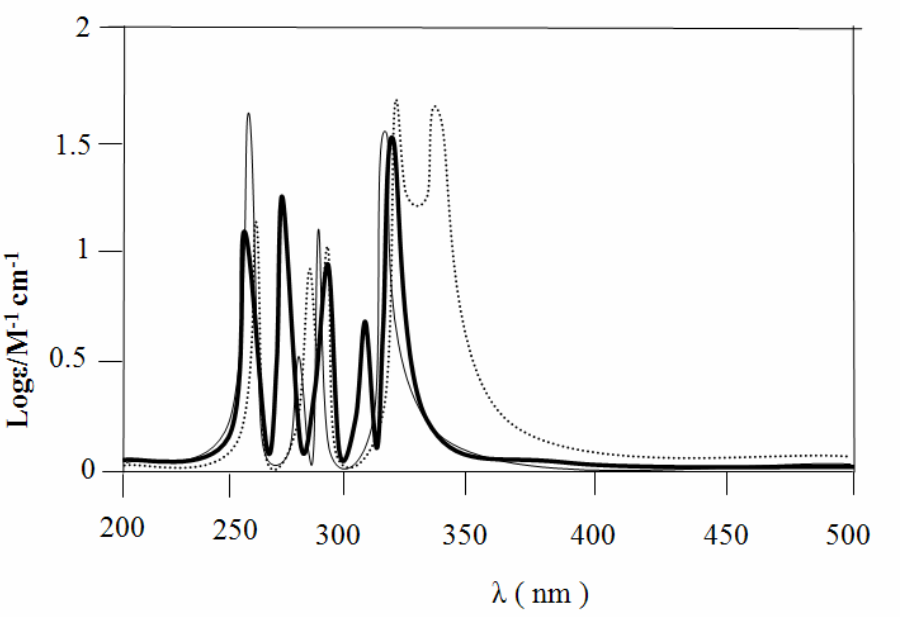


Figure 5. The electronic absorption spectra of Ligand **3f** in: 1,4-Dioxane (bold-black line), DMF (thin-black line) and DMSO (striped-black line).

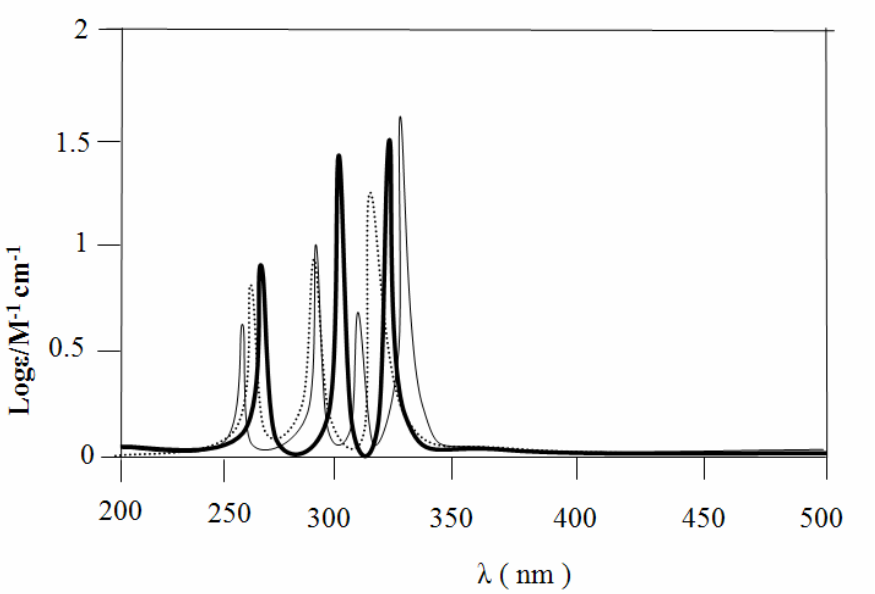


Figure 6. The electronic absorption spectra of Ligand **3f** in: MeOH (striped-black line), MeOH+KOH (bold-black line) and MeOH+HCl (thin-black line).

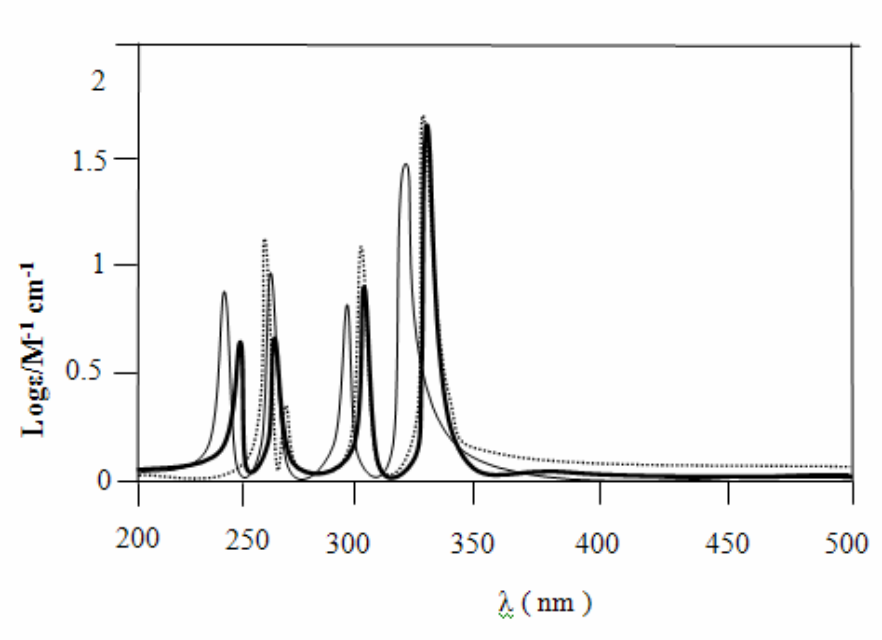


Figure 7. The electronic absorption spectra of Ligand **3h** in: 1,4-Dioxane (bold-black line), DMF (thin-black line) and DMSO (striped-black line).

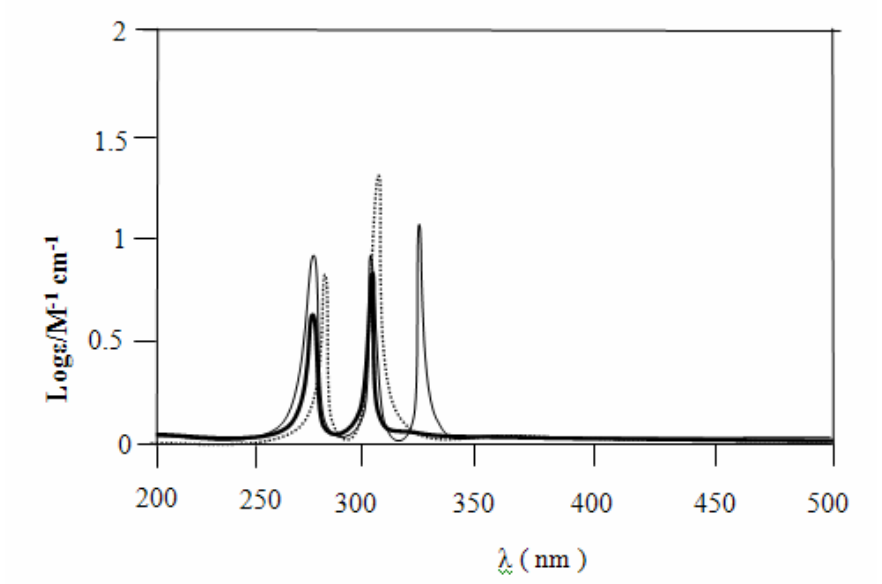


Figure 8. The electronic absorption spectra of Ligand **3h** in: MeOH (striped-black line), MeOH+KOH (bold-black line) and MeOH+HCl (thin-black line).

Experimental Section

General Procedures. Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. ^{1}H- and ^{13}C-NMR spectra were recorded on a Varian-Mercury 200 MHz spectrometer. The IR spectra were measured as potassium bromide pellets using a Perkin-Elmer 1600 series FTIR spectrometer. Elemental analyses were carried out on a CHNO rapid elemental analyzer Hewlett-Packard 185 for C, H and N and results are with in 0.4% of the therotical values. UV/Vis spectra were recorded by means of a Unicam UV2-100 spectrophotometer. The MS spectra were measured with a Micromass Quattro LC/ULTIMA LC-MS/MS spectrometer in the positive ion mode using pyridine-methanol as solvent. All the chemicals were obtained from Fluka Chemie AG Buchs (Switzerland). Compound **2b** has already been published in Acta Crystallographica.[25]

General method for the synthesis bis aldehydes and bis ketone 2

To a solution of hydroxy aldehyde and ketone derivatives (0.1 mol) in absolute ethanol (50 ml) were added KOH (0.1 mol) and *trans*-1,4-dichloro-2-butene **1** (0.025 mol). After the mixture was refluxed and stirred for 18 hours, the solution was filtered and the solid obtained. It was washed with deionized water, ethanol and diethyl ether. The precipitate formed was recrystallized from appropriate solvent to afford the desired compound.

(*E*)-6,6'-[But-2-ene-1,4-diylbis(oxy)]bis(3-bromobenzaldehyde) (2a). The solid obtained was washed with H_2O and recrystallized, (yield: 32%); mp 216 ^{o}C (from DMSO) (Found: C, 47.56; H, 3.12. $C_{18}H_{14}Br_2O_4$ requires C, 47.61; H, 3.11%); IR (KBr) (ν, cm^{-1}), 3103 (Ar-CH), 2766-2869 (CHO), 1678 (C=O); ^{1}H-NMR (DMSO-d_6) δ (ppm) 4.80 (s, 4H, O-CH_2), 6.18 (s, 2H, -HC=CH-), Ar-H [7.20-7.24 (d ,2H), 7.75 (s, 2H), 7.75-7.79 (d, 2H)], 10.30 (s, 2H, CHO); ^{13}C-NMR (DMSO-d_6) δ (ppm) 68.08 (O-CH_2), Ar-C: [112.52 (C), 116.64 (CH), 125.79 (C), 129.28 (CH), 138.24 (CH), 159.28 (C)], 127.78 (-HC=CH-), 188.03 (C=O); MS(ESI-*m/z*): $(M+Na+1)^{+}$: 478; Anal. for $C_{18}H_{14}Br_2O_4$ (Mw 454.11).

(*E*)-2,2'-[But-2-ene-1,4-diylbis(oxy)]di-1-naphthaldehyde (2c). The solid obtained was washed with H_2O and recrystallized, (yield: 57%); mp 220 ^{o}C (from DMF-MeCN, 1:1) (Found: C, 78.69; H, 5.14. $C_{26}H_{20}O_4$ requires C, 78.77; H, 5.09%); IR (KBr) (ν, cm^{-1}), 3075 (Ar-CH), 2793-2875 (CHO), 1668 (C=O); ^{1}H-NMR (DMSO-d_6) δ (ppm) 4.98 (s, 4H, O-CH_2), 6.26 (s, 2H, -HC=CH-), Ar-H [7.44-7.51 (t, 2H), 7.56-7.69 (m, 4H), 7.91-7.95 (d, 2H), 8.21-8.26 (d, 2H), 9.09-9.14 (d, 2H)], 10.83 (s, 2H, CHO); ^{13}C-NMR (DMSO-d_6) δ (ppm) 68.71 (O-CH_2), Ar-C: [114.89 (C), 115.78 (CH), 123.77 (CH), 124.65 (CH), 128.08 (CH), 128.33 (C), 129.66 (CH), 130.54 (C),137.69 (CH), 162.92 (C)], 128.50 (-HC=CH-), 191.20 (C=O); MS(ESI-*m/z*): $(M+Na)^{+}$: 419.27; Anal. for $C_{26}H_{20}O_4$ (Mw 396.43).

(*E*)-1,1'-{4,4'-[But-2-ene-1,4-diylbis(oxy)]bis(4,1-phenylene)}diethanone (2d). The solid obtained was washed with H_2O and recrystallized, (yield: 56%); mp 163 ^{o}C (from acetone-EtOH, 1:1) (Found: C, 74.12; H, 6.19. $C_{20}H_{22}O_4$ requires C, 74.06; H, 6.21%); IR (KBr) (ν, cm^{-1}), 3065 (Ar-CH), 1671 (C=O); ^{1}H-NMR (DMSO-d_6) δ (ppm) 2.52 (s, 6H, CH_3), 4.73 (s, 4H, O-CH_2), 6.10 (s, 2H, -HC=CH-), Ar-H [7.04-7.08 (d, 4H), 7.90-7.94 (d, 4H)]; ^{13}C-NMR (DMSO-d_6) δ (ppm) 26.39 (CH_3), 67.62 (O-CH_2), Ar-C: [114.33 (CH), 130.57 (C), 130.63 (CH), 162.24 (C)],

128.03 (-HC=CH-), 193.64 (C=O); MS(ESI-*m/z*): $(M+Na+2)^+$: 349.15; Anal. for $C_{20}H_{22}O_4$ (Mw 324.14).

General method for the synthesis of bis thiosemicarbazone 3

Compounds **2a-d** (0.0025 mol) and thiosemicarbazite or 4-methyl thiosemicarbazite (0.010 mol) were heated to 160 °C without solvent in an oil bath with stirring for 4 h. DMF was added to the reaction content and dissolved. Then water was added to the solution and a solid precipitated. The solution was filtered and the solid obtained was washed ethanol. The precipitated solid was recrystallized from appropriate solvent to afford the desired compound.

(2*E*,2'*Z*)-2,2'-[6,6'-(*E*)-But-2-ene-1,4-diylbis(oxy)bis(3-bromo-6,1-phenylene)]bis(methan -1-yl-1-ylidene)bis(hydrazinecarbothioamide) (3a). The solid obtained was washed with H_2O and recrystallized, (yield: 68%); mp 258 ^oC (from DMF-EtOH-H_2O, 1:2:1) (Found: C, 40.05; H, 3.32; N, 13,97. $C_{20}H_{20}Br_2N_6O_2S_2$ requires C, 40.01; H, 3.36; N, 14.00%); IR (KBr) (ν, cm^{-1}), 3150-3263 (NH_2), 3149 (-NH-), 3016 (Ar-CH), 1592 (C=N); ^{1}H-NMR (DMSO-d_6) δ (ppm) 4.67 (s, 4H, O-CH_2), 6.19 (s, 2H, HC=CH-), Ar-H [7.03-7.04 (d, 2H), 7.48-7.53 (d, 2H), 8.24 (s, 2H)], 8.46 (s, 2H, CH=N), 8.24 (s, 2H, NH_2), 8.37 (s, 2H, NH_2), 11.56 (s, 2H, -NH); ^{13}C-NMR (DMSO-d_6) δ (ppm) 67.72 (O-CH_2), Ar-C [112.98 (C), 114.89 (CH), 124.52 (C), 126.99 (CH), 128.02 (CH), 155.55 (C)], 133.14 (CH=CH), 136.13 (CH=N), 177.76 (C=S); MS(ESI-*m/z*): $(M+1)^+$: 599.01; Anal. for $C_{20}H_{20}Br_2N_6O_2S_2$ (Mw 597.95).

(2*Z*,2'*Z*)-2,2'-[4,4'-(*E*)-But-2-ene-1,4-diylbis(oxy)bis(3-methoxy-4,1-phenylene)]bis-(methan-1-yl-1-ylidene)bis(hydrazinecarbothioamide) (3b). The solid obtained was washed with H_2O and recrystallized, (yield: 61%); mp 205-206 ^oC (from DMF-EtOH-H_2O, 1:2:1) (Found: C, 52.51, H: 5.26, N: 16.81. $C_{22}H_{26}N_6O_4S_2$ requires C, 52.57; H, 5.21; N, 16.72%); IR (KBr) (ν, cm^{-1}), 3155-3269 (NH_2), 3155 (-NH-), 3037 (Ar-CH), 1599 (C=N). ^{1}H-NMR (DMSO-d_6) δ (ppm) 3.83 (s, 6H, OCH_3), 4.63 (s, 4H, O-CH_2), 6.08 (s, 2H, -HC=CH-), Ar-H [6.96-7.00 (d, 2H), 7.11-7.15 (d, 2H), 7.54 (s, 2H)], 7.97 (s, 2H, CH=N), 8.05 (s, 2H, NH_2), 8.17 (s, 2H, NH_2), 11.34 (s, 2H, -NH); ^{13}C-NMR (DMSO-d_6) δ (ppm) 55.55 (OCH_3), 67.59 (O-CH_2), Ar-C [108.49 (CH), 112.36 (CH), 121.91 (CH), 126.99 (C), 149.14 (C), 149.19 (C)], 128.33 (CH=CH), 142.30 (CH=N), 177.34 (C=S); MS(ESI-*m/z*): $(M+1)^+$: 503.32; Anal. for $C_{22}H_{26}N_6O_4S_2$ (Mw 502.15).

(2*E*,2'*Z*)-2,2'-[2,2'-(*E*)-But-2-ene-1,4-diylbis(oxy)bis(naphthalene-2,1-diyl)]bis(methan-1-yl-1-ylidene)bis(hydrazinecarbothioamide) (3c). The solid obtained was washed with H_2O and recrystallized, (yield: 42%); mp 217 ^oC (from DMF-EtOH, 1:1) (Found: C, 61.91; H, 4.31; N, 15.54. $C_{28}H_{26}N_6O_4S_2$ requires C, 61.97; H, 4.83; N, 15.49%); IR (KBr) (ν, cm^{-1}), 3242-3152 (NH_2), 3150 (-NH-), 3054 (Ar-CH), 1590 (C=N); ^{1}H-NMR (DMSO-d_6) δ (ppm) 4.87 (s, 4H, O-CH_2), 6.26 (s, 2H, -HC=CH-), Ar-H [7.44-7.58 (m, 8H), 7.91-7.98 (bs, 4H)], 8.97 (s, 2H, CH=N), 8.29 (s, 4H, NH_2), 11.68 (s, 2H, -NH); ^{13}C-NMR (DMSO-d_6) δ (ppm) 65.45 (O-CH_2), Ar-C [113.63 (C), 114.48 (CH), 123.74 (CH), 125.49 (CH), 127.91 (CH), 128.32 (CH), 128.83 (C), 131.01 (CH), 132.25 (C), 156.95 (C)], 128.57 (CH=CH), 145.79(CH=N), 177.74 (C=S); MS(ESI-*m/z*): $(M+1)^+$: 543.27; Anal. for $C_{28}H_{26}N_6O_4S_2$ (Mw 542.16).

(2*Z*,2'*Z*)-2,2'-[1,1'-(4,4'-(*E*)-But-2-ene-1,4-diylbis(oxy)bis(4,1-phenylene)]bis(ethan-1-yl-1-ylidene))bis(hydrazinecarbothioamide) (3d). The solid obtained was washed with H_2O and recrystallized, (yield: 58%); mp 229-230 ^oC (from DMSO-EtOH, 1:1) (Found: C, 56.09; H, 5.61; N, 17.89. $C_{22}H_{26}N_6O_2S_2$ requires C, 56.15; H, 5.57; N, 17.86%); IR (KBr) (ν, cm^{-1}), 3139-3224

(NH_2), 3140 (-NH-), 3043 (Ar-CH), 1598 (C=N). ^{1}H-NMR (DMSO-d_6) δ (ppm) 2.24 (s, 6H, CH_3), 4.63 (s, 4H, O-CH_2), 6.05 (s, 2H, -HC=CH-), Ar-H [6.90-6.94 (d, 4H), 7.85-7.89 (d, 4H)], 7.89 (s, 2H, NH_2), 8.22 (s, 2H, NH_2), 10.11 (s, 2H, -NH); ^{13}C-NMR (DMSO-d_6) δ (ppm) 13.75 (CH_3), 67.06 (O-CH_2), Ar-C [114.11 (CH), 128.04 (C), 130.06 (CH), 158.96 (C)], 128.20 (CH=CH), 147.63 (CH=N), 178.43 (C=S); MS(ESI-*m/z*): $(M+1)^+$: 471.29; Anal. for $C_{22}H_{26}N_6O_2S_2$ (Mw 470.16).

(2*E*,2'*Z*)-2,2'-[6,6'-(*E*)-But-2-ene-1,4-diylbis(oxy)bis(3-bromo-6,1-phenylene)]bis-(methan-1-yl-1-ylidene)bis(*N*-methylhydrazinecarbothioamide) (3e). The solid obtained was washed with H_2O and recrystallized, (yield: 73%); mp 254 °C (from DMSO-EtOH, 1:1) (Found: C, 41.99; H, 3.88; N, 13.42. $C_{22}H_{24}Br_2N_6O_2S_2$ requires C, 42.05; H, 3.85; N, 13.37%); IR (KBr) (ν, cm^{-1}), 3133-3310 (-NH-), 3071 (Ar-CH), 1585 (C=N); ^{1}H-NMR (DMSO-d_6) δ (ppm) 3.01-3.03 (d, 6H, -NCH_3), 4.69 (s, 4H, O-CH_2), 6.19 (s, 2H, -HC=CH-), Ar-H [7.04-7.08 (dd, 2H), 7.48-7.54 (dd, 2H), 8.31-8.32 (d, 2H)], 8.45 (s, 2H, CH=N), 8.64-8.66 (d, 2H, -NH-CH_3), 11.63 (s, 2H, -NH); ^{13}C-NMR (DMSO-d_6) δ (ppm) 30.73 (-NCH_3), 67.75 (O-CH_2), Ar-C [112.94 (C), 114.98 (CH), 124.62 (C), 127.03 (CH), 133.09 (CH), 155.54 (C)], 127.76 (HC=CH), 135.67 (CH=N), 177.47 (C=S); MS(ESI-*m/z*): $(M+1)^+$: 626.94; Anal. for $C_{22}H_{24}Br_2N_6O_2S_2$ (Mw 625.98).

(2*Z*,2'*Z*)-2,2'-[4,4'-(*E*)-But-2-ene-1,4-diylbis(oxy)bis(3-methoxy-4,1-phenylene)]bis-(methan-1-yl-1-ylidene)bis(*N*-methylhydrazinecarbothioamide) (3f). The solid obtained was washed with H_2O and recrystallized, (yield: 65%); mp 202 °C (from DMF-EtOH, 1:1) (Found: C, 54.28; H, 5.62; N, 15.96. $C_{24}H_{30}N_6O_4S_2$ requires C, 54.32; H, 5.70; N, 15.84%); IR (KBr) (ν, cm^{-1}), 3175-3293 (-NH-), 3065 (Ar-CH), 1602 (C=N); ^{1}H-NMR (DMSO-d_6) δ (ppm) 3.02-3.04 (d, 6H, -NCH_3), 3.84 (s, 6H, OCH_3), 4.64 (s, 4H, O-CH_2), 6.09 (s, 2H, -HC=CH-), Ar-H [6.98-7.02 (d, 2H), 7.18-7.21 (d, 2H), 7.47 (s, 2H)], 7.97 (s, 2H, CH=N), 8.42-8.44 (d, 2H, -NH-CH_3), 11.40 (s, 2H, -NH); ^{13}C-NMR (DMSO-d_6) δ (ppm) 30.73 (-NCH_3), 55.61 (OCH_3), 67.64 (O-CH_2), Ar-C [109.01 (CH), 112.55 (CH), 121.54 (CH), 127.06 (C), 149.10 (C), 149.17 (C)], 128.37 (HC=CH), 141.89 (CH=N), 177.30 (C=S); MS(ESI-*m/z*): $(M+1)^+$: 531.35; Anal. for $C_{24}H_{30}N_6O_4S_2$ (Mw 530.18).

(2*E*,2'*Z*)-2,2'-[2,2'-(*E*)-But-2-ene-1,4-diylbis(oxy)bis(naphthalene-2,1-diyl)]bis(methan-1-yl-1-ylidene)bis(*N*-methylhydrazinecarbothioamide) (3g). The solid obtained was washed with H_2O and recrystallized, (yield: 72%); mp 228 °C (from DMF-EtOH, 1:1) (Found: C, 63.02; H, 5.37; N, 14.68. $C_{30}H_{30}N_6O_2S_2$ requires C, 63.13; H, 5.30; N, 14.73%); IR (KBr) (ν, cm^{-1}), 3377-3162 (-NH-), 3039 (Ar-CH), 1622 (C=N); ^{1}H-NMR (DMSO-d_6) δ (ppm) 3.05-3.07 (d, 6H, -NCH_3), 4.87 (s, 4H, O-CH_2), 6.27 (s, 2H, HC=CH-), Ar-H [7.39-7.64 (m, 6H), 7.88-8.02 (m, 4H), 8.89-8.94 (d, 2H)], 8.87 (s, 2H, CH=N), 8.14-8.16 (d, 2H, -NH-CH_3), 11.67 (s, 2H, -NH); ^{13}C-NMR (DMSO-d_6) δ (ppm) 31.06 (-NCH_3), 68.68 (O-CH_2), Ar-C [114.38 (C), 114.78 (CH), 123.98 (CH), 125.47 (CH), 127.98 (CH), 128.06 (CH), 128.66 (C), 130.60 (CH), 132.02 (C), 156.54 (C)], 128.24 (HC=CH), 140.69 (CH=N), 177.45 (C=S); MS(ESI-*m/z*): $(M+1)^+$:571.25; Anal. for $C_{30}H_{30}N_6O_2S_2$ (Mw 570.19).

(2*Z*,2'*Z*)-2,2'-{1,1'-[4,4'-(*E*)-But-2-ene-1,4-diylbis(oxy)bis(4,1-phenylene)]bis(ethan-1-yl-1-ylidene)}bis(*N*-methylhydrazinecarbothioamide) (3h). The solid obtained was washed with H_2O and recrystallized, (yield: 60%); mp 246-247 °C (from DMF-EtOH, 1:2) (Found: C, 57.75; H, 6.08; N, 16.79. $C_{24}H_{30}N_6O_2S_2$ requires C, 57.81; H, 6.06; N, 16.85%); IR (KBr) (ν, cm^{-1}),

3313-3175 (-NH-), 3048 (Ar-CH), 1602 (C=N); ^{1}H-NMR (DMSO-d_6) δ (ppm) 2.27 (s, 6H, CH_3), 3.04-3.06 (d, 6H, -NCH_3), 4.66 (s, 4H, O-CH_2), 6.09 (s, 2H, -HC=CH-), Ar-H [6.95-6.99 (d, 4H), 7.88-7.93 (d, 4H)], 8.43-8.45 (d, 2H, -NH-CH_3), 10.18 (s, 2H, -NH); ^{13}C-NMR (DMSO-d_6) δ (ppm) 13.74 (CH_3), 30.93 (-NCH_3), 67.07 (O-CH_2), Ar-C: [114.09 (CH), 127.98 (C), 130.11 (CH), 158.91 (C)], 128.20 (HC=CH), 147.31 (CH=N), 178.13 (C=S); MS(ESI-*m/z*): $(M+1)^+$: 499.28; Anal. for $C_{24}H_{30}N_6O_2S_2$ (Mw 498.67).

General method for the synthesis tetra 4-methyl-5-ethoxy carbonyl-1,3-thiazole 4

To a solution of **3a-h** compounds (0.5 mmol) in absolute ethanol (60 ml) were added ethyl-2-chloro-acetoacetate (2.0 mmol). After the mixture was refluxed and stirred for 80 h, the solution was filtered and the solid obtained was washed with ethanol and deionized water. The precipitated solid was recrystallized from appropriate solvent to afford the desired compound.

(*Z*)-Ethyl 2-((*Z*)-(5-bromo-2-((*E*)-4-(4-bromo-2-((*E*)-((*Z*)-(5-(ethoxycarbonyl)-4-methyl-thiazol-2(3*H*)-ylidene)hydrazono)methyl)phenoxy)but-2-enyloxy)benzylidene)hydrazono)-4-methyl- 2,3-dihydrothiazole-5-carboxylate (4a). The solid obtained was washed with H_2O and recrystallized, (yield: 48%); mp 217 ^{o}C (from DMF-EtOAc, 1:2) (Found: C, 46.75; H, 3.96; N, 10.19. $C_{32}H_{32}Br_2N_6O_6S_2$ requires C, 46.84; H, 3.93; N, 10.24%; IR (KBr) (ν, cm^{-1}), 3153 (-NH-), 3049 (Ar-CH), 1682 (C=O), 1592 (C=N), 1089 (OCH_2CH_3). ^{1}H-NMR (DMSO-d_6) δ (ppm) 1.23-1.30 (t, 6H, $OCH_2C\underline{H}_3$), 2.47 (s, 6H, thiazole-CH_3), 4.16-4.26 (q, 4H, $OC\underline{H}_2CH_3$), 4.73 (s, 4H, O-CH_2), 6.14 (s, 2H, -HC=CH-), Ar-H [7.08-7.12 (d, 4H), 7.51-7.57 (dd, 2H), 7.83-7.84 (d, 2H)], 8.39 (s, 2H, CH=N), 12.41 (s, 2H, -NH); ^{13}C-NMR (DMSO-d_6) δ (ppm) 12.52 ($OCH_2\underline{C}H_3$), 14.22 (thiazole-CH_3), 60.23 ($O\underline{C}H_2CH_3$), 65.94 (O-CH_2), Ar-C [113.92 (C), 114.17 (CH), 124.52 (C), 126.61 (CH), 128.06 (CH), 155.67 (C)], thiazole-C [109.25 (C), 148.14 (C), 161.89 (C)], 132.29 (HC=CH), 147.75 (CH=N), 168.50 (C=O); MS(ESI-*m/z*): (M+ Na)$^+$: 843.50; Anal. for $C_{32}H_{32}Br_2N_6O_6S_2$ (Mw 820.57).

(2*Z*,2'*Z*)-Diethyl 2,2'-{(2*Z*,2'*Z*)-[4,4'-(*E*)-but-2-ene-1,4-diylbis(oxy)bis(3-methoxy-4,1-phenylene)] bis(methan-1-yl-1-ylidene)bis(hydrazine-2,1-diylidene)}bis(4-methyl-2,3-dihydrothiazole-5-carboxylate) (4b). The solid obtained was washed with H_2O and recrystallized, (yield: 48%); mp 192 ^{o}C (from DMF-EtOH, 1:1) (Found: C, 56.47; H, 5.28; N, 11.68. $C_{34}H_{38}N_6O_8S_2$ requires C, 56.50; H, 5.30; N, 11.63%); IR (KBr) (ν, cm^{-1}), 3150 (-NH-), 3027 (Ar-CH), 1705 (C=O), 1599 (C=N), 1087 (OCH_2CH_3); ^{1}H-NMR (DMSO-d_6) δ (ppm) 1.23-1.30 (t, 6H, $OCH_2C\underline{H}_3$), 2.47 (s, 6H, thiazole-CH_3), 3.82 (s, 6H, OCH_3), 3.83-4.22 (q, 4H, $OC\underline{H}_2CH_3$), 4.65 (s, 4H, O-CH_2), 6.10 (s, 2H, -HC=CH-), Ar-H [7.01-7.05 (d, 2H), 7.17-7.21 (d, 2H), 7.28 (s, 2H)], 8.02 (s, 2H, CH=N), 12.36 (s, 2H, -NH); ^{13}C-NMR (DMSO-d_6) δ (ppm) 14.20 ($OCH_2\underline{C}H_3$), 16.99 (thiazole-CH_3), 55.31 (OCH_3), 59.92 ($O\underline{C}H_2CH_3$), 67.62 (O-CH_2), Ar-C [108.76 (CH), 112.87 (CH), 120.52 (CH), 126.76 (C), 149.08 (C), 149.13 (C)], thiazole-C [108.57 (C), 158.26 (C), 162.73 (C)], 128.39 (HC=CH), 144.58 (CH=N), 168.84 (C=O); MS(ESI-*m/z*): $(M+1)^+$: 723.37; Anal. for $C_{34}H_{38}N_6O_8S_2$ (Mw 722.83).

((*Z*)-Ethyl 2-((*E*)-((2-((*E*)-4-(1-((*Z*)-((*Z*)-(5-(ethoxycarbonyl)-4-methylthiazol-2(3*H*)-ylid-ene) hydrazono)methyl)naphthalen-2-yloxy)but-2-enyloxy)naphthalen-1-yl)methylene)-hydrazono)-4-methyl-2,3-dihydrothiazole-5-carboxylate (4c). The solid obtained was washed with H_2O and recrystallized, (yield: 56%); mp 203 ^{o}C (from DMF-EtOH, 2:3) (Found C, 62.92; H, 5.06; N, 11.09. $C_{40}H_{38}N_6O_6S_2$ requires C, 62.97; H, 5.02; N, 11.02%); IR (KBr) (ν, cm^{-1}), 3170 (-NH-),

3049 (Ar-CH), 1719 (C=O), 1594 (C=N), 1091 (OCH_2CH_3); ^{1}H-NMR (DMSO-d_6) δ (ppm) 1.23-1.29 (t, 6H, $OCH_2C\underline{H}_3$), 2.47 (s, 6H, thiazole-CH_3), 4.13-4.24 (q, 4H, $OC\underline{H}_2CH_3$), 4.82 (s, 4H, O-CH_2), 6.13 (s, 2H, -HC=CH-), Ar-H [7.24-7.46 (m, 6H), 7.54-7.72 (m, 4H), 8.97-9.43 (d, 2H)], 8.89 (s, 2H, CH=N), 12.39 (s, 4H, -NH); ^{13}C-NMR (DMSO-d_6) δ (ppm) 13.87 ($OCH_2\underline{C}H_3$), 17.04 (thiazole-CH_3), 60.01 ($O\underline{C}H_2CH_3$), 67.56 (O-CH_2), Ar-C [114.40 (C), 118.15 (CH), 124.08 (CH), 125.52 (CH), 127.12 (CH), 128.51 (CH), 128.94 (C), 130.67 (CH), 132.44 (C), 156.89 (C)], thiazole-C: [102.26 (C), 158.85 (C), 161.89 (C)], 130.18 (HC=CH), 146.89 (CH=N), 167.84 (C=O); MS(ESI-*m/z*): $(M+1)^+$: 763.29; Anal. for $C_{40}H_{38}N_6O_6S_2$ (Mw 762.23).

(2*Z*,2'*Z*)-Diethyl 2,2'-((2*Z*,2'*Z*)-(1,1'-(4,4'-(*E*)-but-2-ene-1,4-diylbis(oxy)bis(4,1-phenylene)) bis(ethan-1-yl-1-ylidene))bis(hydrazine-2,1-diylidene))bis(4-methyl-2,3-dihydrothiazole-5-carboxylate) (4d). The solid obtained was washed with H_2O and recrystallized, (yield: 53%; mp 144-145 °C (from DMF-Et_2O, 1:2) (Found: C, 59.07; H, 5.56; N, 12.21. $C_{34}H_{38}N_6O_6S_2$ requires C, 59.11; H, 5.54; N, 12.17%); IR (KBr) (ν, cm^{-1}), 3197 (-NH-), 3052 (Ar-CH), 1712 (C=O), 1611 (C=N), 1103 (OCH_2CH_3); ^{1}H-NMR (DMSO-d_6) δ (ppm) 1.23-1.30 (t, 6H, $OCH_2C\underline{H}_3$), 2.28 (s, 6H, CH_3), 2.48 (s, 6H, thiazole-CH_3), 4.15-4.25 (q, 4H, $OC\underline{H}_2CH_3$), 4.66 (s, 4H, O-CH_2), 6.09 (s, 2H, -HC=CH-), Ar-H [6.99-7.03 (d, 4H), 7.14-7.76 (d, 4H)], 11.69 (s, 2H, -NH); ^{13}C-NMR (DMSO-d_6) δ (ppm) 14.06 (CH_3), 14.22 ($OCH_2\underline{C}H_3$), 16.55 (thiazole-CH_3), 59.92 ($O\underline{C}H_2CH_3$), 67.07 (O-CH_2), Ar-C [114.12 (CH), 127.25 (C), 130.06 (CH), 156.36 (C)], thiazole-C [109.64 (C), 158.89 (C), 161.85 (C)], 128.29 (HC=CH), 147.89 (CH=N), 165.22 (C=O); MS(ESI-*m/z*): $(M+1)^+$: 691.35; Anal. for $C_{34}H_{38}N_6O_6S_2$ (Mw 690.23).

(*Z*)-Ethyl 2-((*Z*)-(5-bromo-2-((*E*)-4-(4-bromo-2-((*E*)-((*Z*)-(5-(ethoxycarbonyl)-3,4-dimethylthiazol-2(3*H*)- ylidene)hydrazono)methyl)phenoxy)but-2-enyloxy)benzylidene)hydrazono)-3,4-dimethyl-2,3-dihydrothiazole-5-carboxylate (4e). The solid obtained was washed with H_2O and recrystallized, (yield: 56%); mp 257 °C (from DMSO) (Found: C, 48.07; H, 4.31; N, 9.87. $C_{34}H_{36}Br_2N_6O_6S_2$ requires C, 48.12; H, 4.28; N, 9.90%); IR (KBr) (ν, cm^{-1}), 3042 (Ar-CH), 1698 (C=O), 1598 (C=N), 1087 (OCH_2CH_3); ^{1}H-NMR (DMSO-d_6) δ (ppm) 1.32-1.39 (t, 6H, $OCH_2C\underline{H}_3$), 2.57 (s, 6H, thiazole-CH_3), 3.47 (s, 6H, N-CH_3), 4.24-4.34 (q, 4H, $OC\underline{H}_2CH3$), 4.59 (s, 4H, O-CH_2), 6.06 (s, 2H, -HC=CH-), Ar-H [6.72-6.77 (d, 2H), 7.26-7.40 (dd, 2H), 8.17-8.18 (d, 2H)], 8.66 (s, 2H, CH=N); ^{13}C-NMR (DMSO-d_6) δ (ppm) 12.83 ($OCH_2\underline{C}H_3$), 14.43 (thiazole-CH_3), 31.60 (N-CH_3), 60.85 ($O\underline{C}H_2CH_3$), 68.36 (O-CH_2), Ar-C [113.88 (C), 114.23 (CH), 126.19 (C), 128.08 (CH), 129.28 (CH), 155.80 (C)], thiazole-C [103.86 (C), 146.64 (C), 162.19 (C)], 133.12 (HC=CH), 147.32 (CH=N), 168.31 (C=O); MS(ESI-*m/z*): $(M+1)^+$: 849.29; Anal. for $C_{34}H_{36}Br_2N_6O_6S_2$ (Mw 848.62).

(2*Z*,2'*Z*)-Diethyl 2,2'-((2*Z*,2'*Z*)-(4,4'-(*E*)-but-2-ene-1,4-diylbis(oxy)bis(3-methoxy-4,1-phenylene))bis (methan-1-yl-1-ylidene)bis(hydrazine-2,1-diylidene))bis(3,4-dimethyl-2,3-dihydrothiazole-5-carboxylate) (4f). The solid obtained was washed with H_2O and recrystallized, (yield: 54%); mp 232-233 °C (from DMF-EtOH, 1:1) (Found: C, 57.57; H, 5.69; N, 11.25. $C_{36}H_{42}N_6O_8S_2$ requires C, 57.58; H, 5.64; N, 11.19%); IR (KBr) (ν, cm^{-1}), 3082 (Ar-CH), 1690 (C=O), 1601 (C=N), 1088 (OCH_2CH_3); ^{1}H-NMR (DMSO-d_6) δ (ppm) 1.22-1.29 (t, 6H, $OCH_2C\underline{H}_3$), 2.55 (s, 6H, thiazole-CH_3), 3.42 (s, 6H, N-CH_3), 3.82 (s, 6H, OCH_3), 4.19-4.23 (q, 4H, $OC\underline{H}_2CH3$), 4.65 (s, 4H, O-CH_2), 6.09 (s, 2H, -HC=CH-), Ar-H [7.01-7.05 (d, 2H), 7.22-7.26 (d, 2H), 7.35 (s, 2H)], 8.27 (s, 2H, CH=N); ^{13}C-NMR (DMSO-d_6) δ (ppm) 12.31 ($OCH_2\underline{C}H_3$), 14.15 (thiazole-CH_3), 31.26 (N-CH_3), 55.39 (OCH_3), 60.17 ($O\underline{C}H_2CH_3$), 65.63 (O-CH_2), Ar-C [109.39 (CH),

114.06 (CH), 120.93 (CH), 128.31 (C), 149.28 (C), 153.24 (C)], thiazole-C [101.13 (C), 160.87 (C), 165.69 (C)], 131.23 (HC=CH), 148.02 (CH=N), 169.38 (C=O); MS(ESI-*m/z*): $(M+Na)^+$: 773.54; Anal. for $C_{36}H_{42}N_6O_8S_2$ (Mw 750.88).

(*Z*)-Ethyl 2-((*E*)-((2-((*E*)-4-(1-((*Z*)-((*Z*)-(5-(ethoxycarbonyl)-3,4-dimethylthiazol-2(3*H*)-ylidene)hydrazono)methyl)naphthalen-2-yloxy)but-2-enyloxy)naphthalen-1-yl)methyl-ene) hydrazono)-3,4-dimethyl-2,3-dihydrothiazole-5-carboxylate (4g). The solid obtained was washed with H_2O and recrystallized, (yield: 49%); mp 179 °C (from DMF-Et_2O, 1:2) (Found: C, 63.71; H, 5.39; N, 10.70. $C_{42}H_{42}N_6O_6S_2$ requires C, 63.78; H, 5.35; N, 10.63%); IR (KBr) (ν, cm^{-1}), 3038 (Ar-CH), 1702 (C=O), 1590 (C=N), 1095 (OCH_2CH_3); ^{1}H-NMR (DMSO-d_6) δ (ppm) 1.23-1.30 (t, 6H, $OCH_2C\underline{H}_3$), 2.54 (s, 6H, thiazole-CH_3), 3.42 (s, 6H, N-CH_3), 4.17-4.24 (q, 4H, $OC\underline{H}_2CH_3$), 4.89 (s, 4H, O-CH_2), 6.22 (s, 2H, -HC=CH-), Ar-H [7.43-7.60 (m, 6H), 7.88-7.99 (m, 4H), 9.27-9.91 (d, 2H)], 9.06 (s, 2H, CH=N); ^{13}C-NMR (DMSO-d_6) δ (ppm) 12.31 ($OCH_2\underline{C}H_3$), 14.00 (thiazole-CH_3), 31.08 (N-CH_3), 60.22 ($O\underline{C}H_2CH_3$), 68.10 (O-CH_2), Ar-C [114.38 (C), 118.02 (CH), 123.43 (CH), 125.22 (CH), 126.02 (CH), 127.77 (CH), 127.88 (C), 127.98 (CH), 130.34 (C), 153.50 (C)], thiazole-C [101.04 (C), 147.97 (C), 161.22 (C)], 130.50 (HC=CH), 147.60 (CH=N), 166.26 (C=O); MS(ESI-*m/z*): $(M+1)^+$: 792.37; Anal. for $C_{42}H_{42}N_6O_6S_2$ (Mw 790.95).

(2*Z*,2'*Z*)-Diethyl 2,2'-[(2*Z*,2'*Z*)-{1,1'-[4,4'-(*E*)-but-2-ene-1,4-diylbis(oxy)bis(4,1-phenylene)] bis(ethan-1-yl-1-ylidene)}bis(hydrazine-2,1-diylidene)]bis(3,4-dimethyl-2,3-dihydro-thiazole- 5-carboxylate) (4h). The solid obtained was washed with H_2O and recrystallized, (yield: 61%); mp 240 °C (from DMF-Et_2O, 1:2) (Found: C, 60.09; H, 5.93; N, 11.66. $C_{36}H_{42}N_6O_6S_2$ requires C, 60.15; H, 5.89; N, 11.69%); IR (KBr) (ν, cm^{-1}), 3054 (Ar-CH), 1672 (C=O), 1590 (C=N), 1095 (OCH_2CH_3); ^{1}H-NMR (DMSO-d_6) δ (ppm) 1.19-1.26 (t, 6H, $OCH_2C\underline{H}_3$), 2.34 (s, 6H, CH_3), 2.53 (s, 6H, thiazole-CH_3), 3.43 (s, 6H, N-CH_3), 4.16-4.19 (q, 4H, $OC\underline{H}_2CH_3$), 4.63 (s, 4H, O-CH_2), 6.07 (s, 2H, -HC=CH-), Ar-H [6.95-6.99 (d, 4H), 7.74-7.79 (d, 4H)]; ^{13}C-NMR (DMSO-d_6) δ (ppm) 12.49 (CH_3), 14.05 ($OCH_2\underline{C}H_3$), 14.17 (thiazole-CH_3), 31.42 (N-CH_3), 60.21 ($O\underline{C}H_2CH_3$), 67.08 (O-CH_2), Ar-C [114.35 (CH), 127.36 (C), 130.74 (CH), 156.21 (C)], thiazole-C [113.48 (C), 158.95 (C), 161.47 (C)], 128.40 (HC=CH), 148.23 (CH=N), 165.13 (C=O); MS(ESI-*m/z*): $(M)^+$: 719.00; Anal. for $C_{36}H_{42}N_6O_6S_2$ (Mw 718.89).

General method for the synthesis bis(1,3,4-thiadiazol-2-amine) 6

(*E*)-1,4-Bis-thiocyanato-but-2-ene **5** (0.05 mol) and thiosemicarbazite or 4-methyl thiosemicarbazite (0.10 mol) in trifluoroacetic acid (5 ml) were refluxed at 60-70 °C for 4 h in oil bath with stirring. The reaction mixture was poured into ice-cold water (200 ml) and neutralized with ammonia. The solid obtained was washed with H_2O and crystallized from an appropriate solvent to afford the desired compound.

5-[(*E*)-4-(5-amino-1,3,4-thiadiazol-2-ylthio)but-2-enylthio]-1,3,4-thiadiazol-2-amine (6k). The solid obtained was washed with H_2O and recrystallized, (yield: 84%); mp 218 °C (from DMF-EtOH, 1:2) (Found: C, 40.13; H, 3.21; N, 26.38. $C_8H_{10}N_6S_4$ requires C, 40.17; H, 3.16; N, 26.39%); IR (KBr) (ν, cm^{-1}), 3153-3287 (Ar-NH_2), 3098 (Ar-CH), 1640 (C=N); ^{1}H-NMR (DMSO-d_6) δ (ppm) 3.69 (s, 4H, S-$C\underline{H}_2$), 5.76 (s, 2H, -HC=CH-), 7.31 (s, 4H, NH_2); ^{13}C-NMR (DMSO-d_6) δ (ppm) 35.77 (S-$\underline{C}H_2$), tiadiazole-C [149.24 (C), 169.70 (C)], 128.96 (-HC=CH-); MS(ESI-*m/z*): $(M+1)^{+1}$: 319.22; Anal. for $C_8H_{10}N_6S_4$ (Mw 318.47).

5-{(*E*)-4-[5-(Methylamino)-1,3,4-thiadiazol-2-ylthio]but-2-enylthio}-*N*-methyl-1,3,4-thiadiazol- 2-amine (6l). The solid obtained was washed with H_2O and recrystallized, (yield: 84%); mp 229 ^oC (from DMF-EtOH, 1:2) (Found: C, 34.59; H, 4.11; N, 24.19. $C_{10}H_{14}N_6S_4$ requires C, 34.66; H, 4.07; N, 24.25%); IR (KBr) (ν, cm^{-1}), 3209 (-NH-), 3087 (Ar-CH), 1602 (C=N); ^{1}H-NMR (DMSO-d_6) δ (ppm) 2.83-2.85 (d, 6H, N-C$\underline{H}_3$), 3.85 (s, 4H, S-C$\underline{H}_2$), 5.89 (s, 2H, -HC=CH-), 7.77-7.79 (d, 2H, NH); ^{13}C-NMR (DMSO-d_6) δ (ppm) 31.11 (-N$\underline{C}H_3$), 35.38 (S-$\underline{C}H_2$), thiadiazole-C [147.89 (C), 170.95 (C)], 129.37 (-HC=CH-); MS(ESI-*m/z*): $(M+1)^{+1}$: 347.63; Anal. for $C_{10}H_{14}N_6S_4$ (Mw 346.52).

Assay of antimicrobial activity

All test microorganisms were obtained from the Hifzissihha Institute of Refik Saydam (Ankara, Turkey) and were as follows: *Escherichia coli* ATCC 35218, *Pseudomonas auroginosa* ATCC 10145, *Klebsiella pneumoniae* ATCC 13883, *Enterococcus faecalis* ATCC 29212, *Staphylococcus aureus* ATCC 25923, *Bacillus cereus* 709 ROMA, and *Candida albicans* ATCC 60193. All the newly synthesized compounds were dissolved in dimethylformamide (DMF) and chloroform ($CHCl_3$) to prepare chemicals stock solution of 4.0-14.0 mg/ml.

Simple susceptibility screening test using agar-well diffusion method[30] as adapted earlier[31] was used. Each microorganism was suspended in Mueller Hinton (MH) (Difco, Detroit, MI) broth and diluted approximately 10^6 colony forming unit (cfu) per ml. They were "flood-inoculated" onto the surface of MH agar and Sabouraud Dextrose Agar (SDA) (Difco, Detriot, MI) and then dried. For *C. albicans* SDA were used. Five-millimeter diameter wells were cut from the agar using a sterile cork-borer, and 50 μl of the extract substances were delivered into the wells. The plates were incubated for 24-48 h at 35°C. Antimicrobial activity was evaluated by measuring the zone of inhibition against the test organism. Ceftazidime (10 μg) and Triflucan (5 μg) were standard drugs. DMF and $CHCl_3$ was used as solved control.

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