

Synthesis and characterizations of some new tetra-thiosemicarbazones and their cyclization reactions; tetra-4-methyl-5-ethoxycarbonyl-2,3-dihydro-1,3-thiazole and tetra-2-acetylamino-4-acetyl-4,5-dihydro-1,3,4-thiodiazole derivatives

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Abstract

Tetra-aldehyde and ketone derivatives (**2a-d**) which were used to obtain tetra thiosemicarbazone compounds **3a-h** were synthesized via the reaction of Ethene-1,1,2,2,-tetra-yl-tetra-methylene-tetra-bromide (**1**) with aldehydes and ketons. Then, tetra-thiosemicarbazone compounds **3a-h** were obtained from the reactions of tetra- aldehyde and keton derivatives (**2a-d**) with thiosemicarbazite and 4-methyl thiosemicarbazite, respectively. In the same way, tetra-4-methyl-5-ethoxycarbonyl-2,3-dihydro-1,3-thiazole compounds **4a-h** were synthesized via the reaction of tetra-thiosemicarbazone compounds **3a-h** with ethyl-2-chloroacetoacetate. Then, tetra-thiosemicarbazone compounds **3a-h** were reacted with acetic anhydride, and yielded tetra-2-acetyl-amino-4-acetyl-4,5-dihydro-1,3,4-thiodiazol compounds (**5a,b,c,e,f,g**). They were characterized by elemental analysis, infrared, ¹H and ¹³C-NMR, mass spectroscopy. Then, the microbial features of all compounds were studied by the known method.

Keywords: Thiosemicarbazone, tetra-4-methyl-5-ethoxycarbonyl-2,3-dihydro-1,3-thiazole, tetra-2-acetylamino-4-acetyl-4,5-dihydro-1,3,4-thiodiazole derivatives, Hantzsch reagent

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 parasitocidal action against *Plasmodium falciparum* and *Trypanasoma cruzi* which are the causative agents of malaria and Chagas's disease, respectively.¹⁻⁴

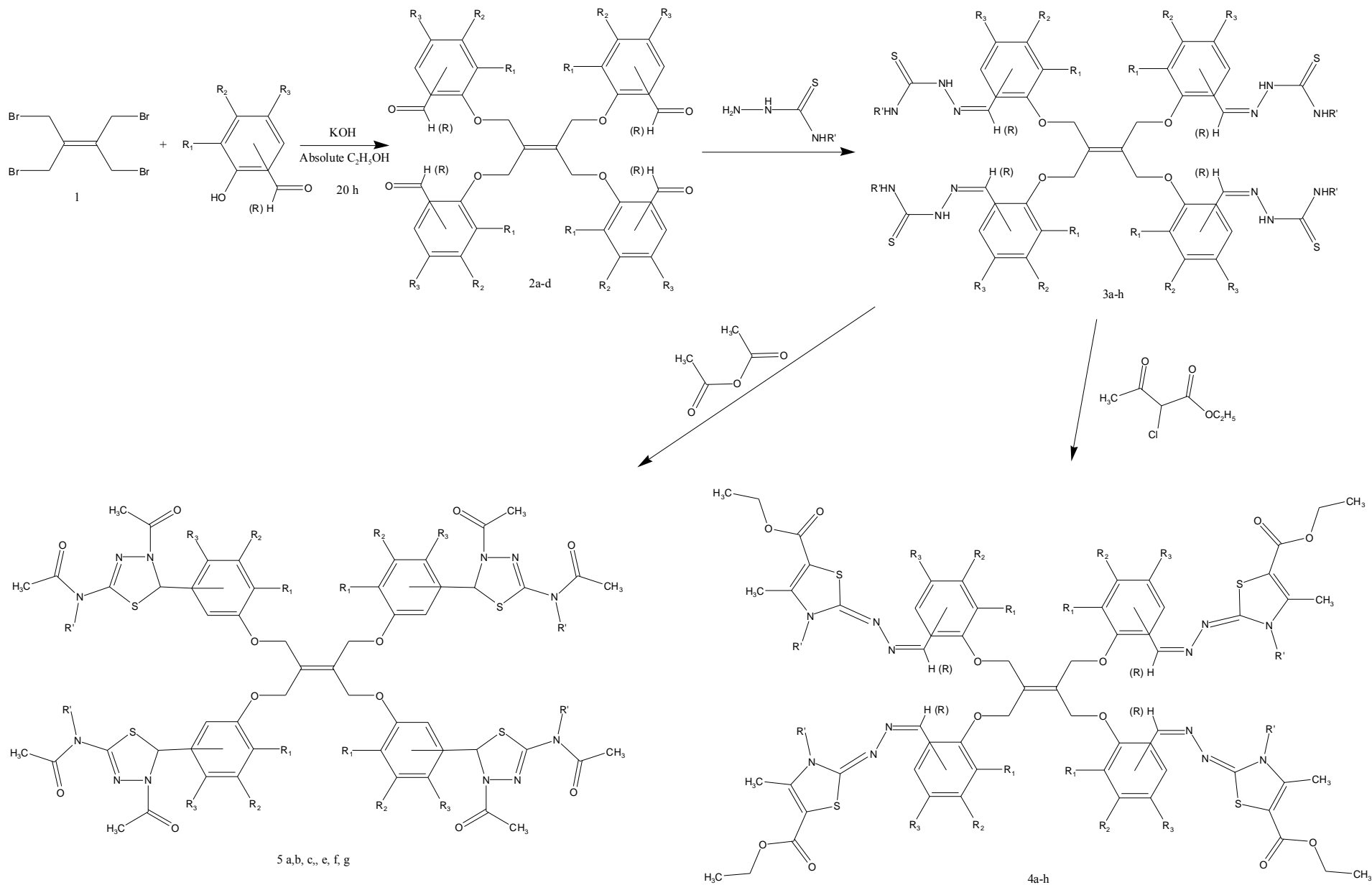
Epilepsy, one of the most frequent neurological disorders, is a major public health issue, affecting about 4% of individuals over their lifetime.⁵ Recent studies revealed that a number of aryl semicarbazones possessed anticonvulsant activity in the maximal electroshock (MES) and

subcutaneous pentylenetetrazole (scPTZ) screens when administered by the intraperitoneal route to mice.⁵⁻¹¹ In recent years, aryl and heteroaryl semicarbazones and thiosemicarbazones have emerged as structurally novel anticonvulsants.¹² Aryl semicarbazides have also been reported to display excellent anticonvulsant activity in mice and rats.¹³ During the past decade, several new drugs have been approved (Rufinamide, Retigabine, Pregabalin, etc.). Despite advances in the drug treatment of epilepsy, a number of limitations of antiepileptic drug therapy continue to exist. Thus the search for new anticonvulsant drugs continues to be an active area of investigation in medicinal chemistry.⁷

Thiosemicarbazones can be used for making electrodes due to formation of easy complexes with some metals. In the previous study, benzyl bis-thiosemicarbazones have been used for the construction of electrodes.¹⁴ In another study, the bis(thiosemicarbazone) complexes of copper have shown special promise as radiopharmaceuticals, as illustrated by a per fusion imaging agent.¹⁵⁻¹⁹ In the recent studies, appear to be a structural class with anti-pox virus activity.²⁰ Isatin derivatives such as methisazone (marboran), the β -thiosemicarbazone of N-methyl isatin, have been described as smallpox chemoprophylactic agents.²¹ Methisazone decreases morbidity and mortality when given to susceptible contacts, but has no direct therapeutic efficacy vs variola and is no longer manufactured as a drug substance.²²

Thiosemicarbazones have been reported to exhibit antituberculosis activity.^{23,24} Besides, 1,3,4-thiadiazoles and 1,3-thiazoles and their derivatives exhibit various biological activities such as antituberculosis,²⁴ antimicrobial,²⁵⁻²⁷ anti-inflammatory,²⁸⁻³⁰ antiviral, anticonvulsant,³¹⁻³² antihypertensive,³³⁻³⁴ local anesthetic,³⁵ anticancer,³⁶⁻³⁷ hypoglycemic,³⁸ and cytotoxic activities, among others.³⁹⁻⁴⁵ 1,3,4-Thiadiazole and related compounds are of great interest in chemistry owing to their bioactivity of certain plant growth regulating effects as well as antimicrobial activity.⁴⁶⁻⁴⁸ Antitubercular activities of thiadiazoles linked with aromatic cycles through the methyleneoxy group have also been reported and compounds of this type have shown inhibition on both cyclooxygenase and 5-lipoxygenase activities.^{28,50} Lee and coworkers have synthesized some thiodiazoles with antihelminthic activities⁵¹. 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.⁵²⁻⁵⁵

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



Scheme 1. Synthetic pathway for the preparation of target compounds (2, 3, 4 and 5).

	a	b	c	d	e	f	g	h	
R'	H	H	H	H	CH ₃	CH ₃	CH ₃	CH ₃	

Results and Discussion

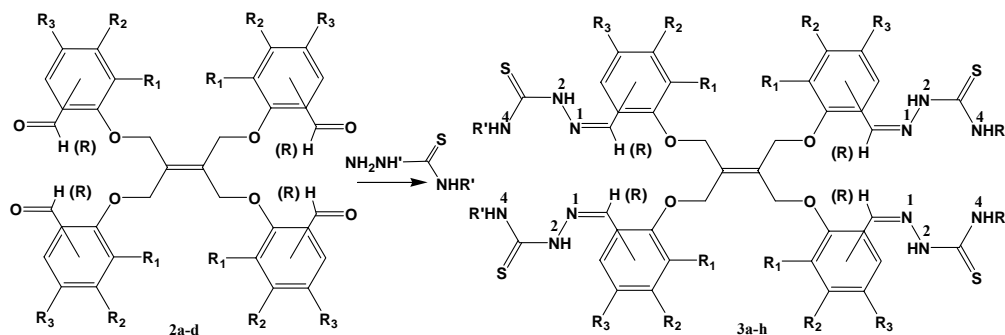
In the first part of this study, tetra-aldehyde and ketone derivatives (**2a-d**) were obtained from the reaction of ethene-1,1,2,2-tetra-yl-tetra-methylene-tetra-bromide (**1**) with aldehydes and ketones in absolute ethanol and KOH in reasonably good yields (Scheme 1).

In the IR spectra of compounds **2a-d**, one sharp absorption band was seen at 1673-1702 cm⁻¹ which belongs to the carbonyl function. $\nu(\text{CHO})$ Fermi doublet stretching frequency and $\nu(\text{C-O-C})$ stretching frequency were observed at 2724-2894 cm⁻¹ and 1167-1245 cm⁻¹ in the IR spectra, respectively.

In the ¹H-NMR spectra of compounds **2a-d** proton signal belonging to methylene group was recorded 4.48-5.44 ppm (-O-CH₂) integrating for eight protons. Aldehyde protons (CHO) were observed at 9.81-10.67 ppm integrating for four protons. In the ¹H-NMR spectra of compound **2d**, no signal derived from the ketone function was observed.

In the ¹³C-NMR the signal of the methylene function of compounds **2a-d**, the OCH₂ group signal was observed at 65-66 ppm. C=O and C=C functions of compounds **2a-d** appeared at 187-196 ppm and 134-135 ppm in the ¹³C-NMR spectra, respectively. ¹H-NMR and ¹³C-NMR spectral data belonging to compounds **2a-d** are presented later in this experimental section.

Tetra-thiosemicarbazones derivatives (**3a-h**) were synthesized via the reaction of tetra aldehyde and ketone derivatives with thiosemicarbazite and 4-methyl-thiosemicarbazite compounds, respectively. (Scheme 2)



Scheme 2

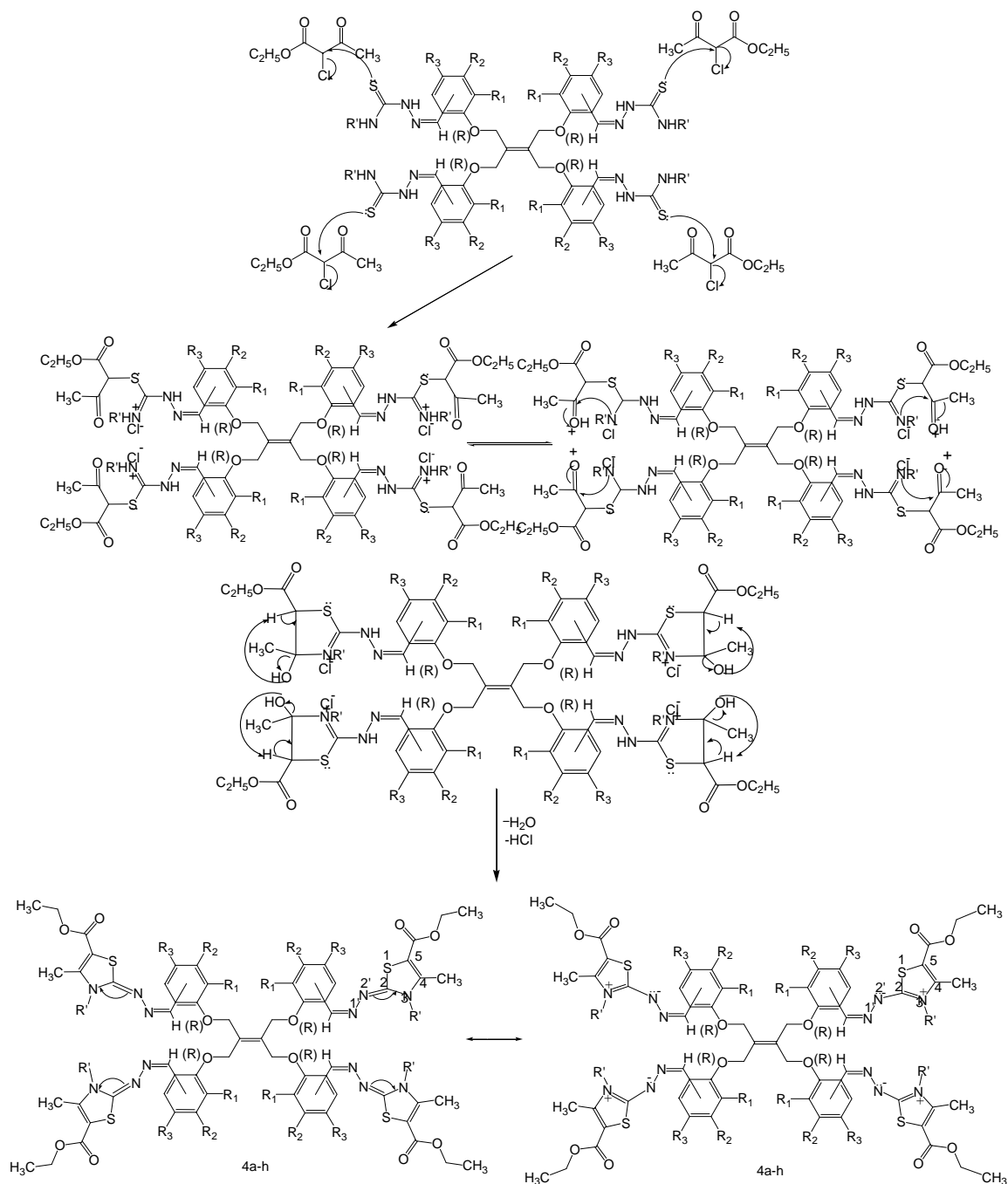
In the IR spectral data of compounds **3a-h**, while signals belonging to the carbonyl group which appeared at 1673-1702 cm^{-1} was disappeared, symmetric and asymmetric stretch bands belonging to the $\nu(-\text{NH}_2)$ group were seen at 3253-3358 cm^{-1} . $\nu(\text{NH})$ and $\nu(\text{CH}=\text{N})$ stretching frequency were observed at 3148-3159 cm^{-1} and 1589-1599 cm^{-1} in the IR spectra, respectively.

In the $^1\text{H-NMR}$ spectra of compounds **3a-h**, the proton signals appearing for **3a-d** compounds were recorded at 8.20-8.29 ppm ($-\text{NH}_2$) integrating for eight protons (controlled by changing with D_2O) and the proton signals appearing for **3e-h** compounds were recorded 8.40-8.84 ppm (NH-CH_3) integrating for four protons (controlled by changing with D_2O). ^2NH protons were observed at 10.13-11.59 ppm integrating for four protons (exchangeable with D_2O). In the $^1\text{H-NMR}$ spectra of compounds **3a-h**, another characteristic proton signal belonging to $\text{CH}=\text{N}$ was observed at 7.99-8.85 ppm integrating for four protons. $\text{CH}=\text{N}$ proton signal for compounds **3d** and **3h** which were keton thiosemicarbazone derivatives was not observed in the $^1\text{H-NMR}$ spectra.

In the $^{13}\text{C-NMR}$ spectral data of compounds **3a-h**, while $\text{C}=\text{O}$ belonging to $^{13}\text{C-NMR}$ signal of compounds **2a-d** which appeared at 187-196 ppm was disappeared, $^{13}\text{C-NMR}$ belonging to $\text{C}=\text{S}$ group for compounds **3a-h** was observed at 177-178 ppm. It was reported that the peak was quite specific spectral data [59-62]. The $^{13}\text{C-NMR}$ signal of $\text{CH}=\text{N}$ function of azomethylene and $\text{C}=\text{C}$ function of compounds **3a-h** appeared at 133-147 ppm and 133-135 ppm, respectively.

4-Methyl-5-ethoxycarbonyl-2,3-dihydro-1,3-thiazole compounds **4a-h** were obtained by using the Hantzsch reaction from the reaction tetra-thiosemicarbazone derivatives (**3a-h**) with ethyl-2-chloro acetoacetate.

This reaction was carried by using the Hantzsch reaction, which is obtained from α -halogeno ketone and aldehyde with thioamide. According to this reaction mechanism, two tautomeric form could be possible, but spectral data and physical parameters show that compounds **4a-h** have exo-imin form in 2-position of thiazole group (Scheme 3)



Scheme 3

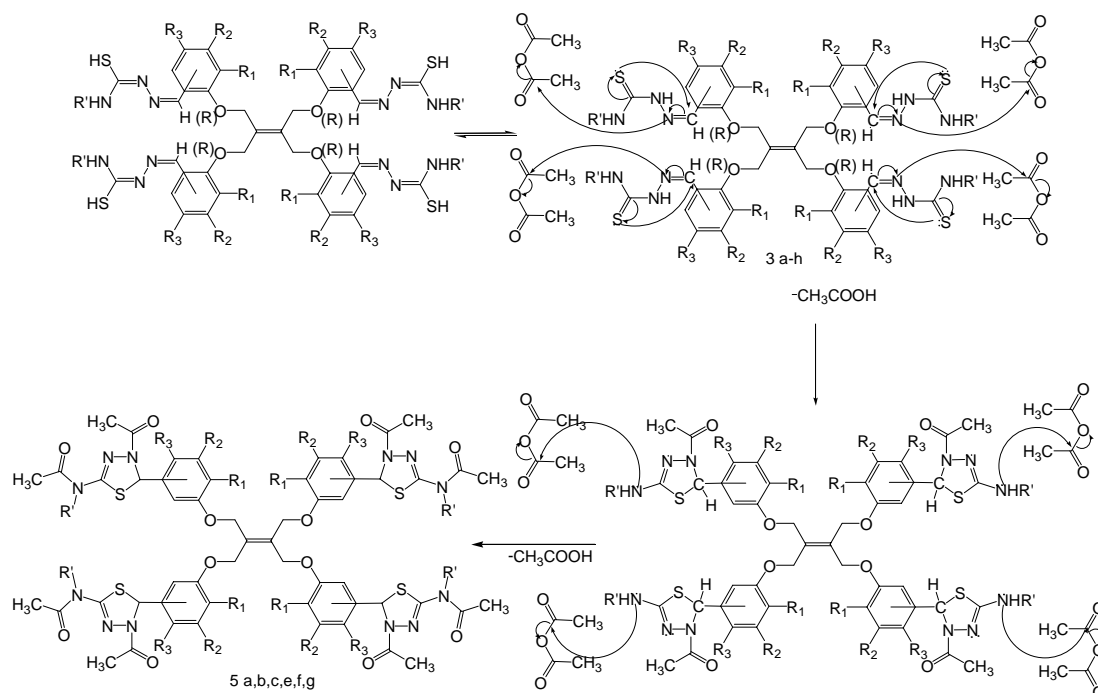
The most important data for the synthesized compounds **4a-h** was seen at 1670-1699 cm^{-1} belonging to $\nu(\text{C}=\text{O})$ group in the IR spectra. $\nu(\text{CH}=\text{N})$ and $\nu(\text{C}-\text{O}-\text{C})$ Stretching frequencies were observed at 1593-1600 cm^{-1} and 1088-1093 cm^{-1} in the IR spectra, respectively.

In the $^1\text{H-NMR}$ spectra of compounds **4a-h** the most characteristic NH proton signal, which was observed for compounds **4a-d**, was the most important evidence performed for 1,3-thiazole

ring. In the $^1\text{H-NMR}$ spectra, the signal belonging to NH group which has acidic character was observed at 11.76-12.41 ppm integrating for four protons like NH signal belonging to hetero ring. NH protons which were seen at 11.76-12.41 ppm can be bound to two alternative position. One of them is ^2N -position, the other is ^3N -position of 1,3-thiazole ring. In the $^1\text{H-NMR}$ spectral data, compounds **4a-h** showed NH proton signal corresponding ^3N -position. In the $^1\text{H-NMR}$ spectra, ^2NH proton signal of thiosemicarbazone was seen at 10.13-11.59 ppm. The spectral data showed that 1,2-dihydro-4-methyl-5-ethoxycarbonyl-1,3-thiazole compounds **4a-h** were obtained. This result is in accordance with literature [22]. In the D_2O exchange for the compounds four NH group signal was disappeared in the $^1\text{H-NMR}$ spectra. CH_3 protons belonging to thiazole ring for compounds **4a-h** appeared at 2.44-2.57 ppm integrating for twelve protons. N-CH_3 proton signals for compounds **4e-h** were seen at 3.10-3.43 ppm integrating for twelve protons. While CH_3 protons belonging to ester appeared at 1.20-1.30 ppm integrating for twelve protons, OCH_2 protons belonging to ester were seen at 4.23-4.53 ppm integrating for eight protons in the $^1\text{H-NMR}$ spectra.

The $^{13}\text{C-NMR}$ signals of compounds **4a-h** carbones of esteric CH_3 and OCH_2 , carbones of thiazole ring CH_3 and O-CH_2 were seen at range 14-66 ppm. This spectral data is the most evidence for sp^3 hybridized carbones. $^{13}\text{C-NMR}$ spectral data belonging to compounds **4a-h** were presented in details at experimental section in this study. While ^5C and ^4C of thiazole ring were observed 101-109 ppm and 146-161 ppm respectively, exo $^2\text{N}=\text{C}$ carbon data of thiazole ring appeared at 161-166 ppm in the $^{13}\text{C-NMR}$ spectra. The most important spectral data is the carbonyl carbon of ethoxy carbonyl connected to thiazole ring. While $\text{C}=\text{S}$ carbon peak which was disappeared for compounds (**3a-h**) was seen at 177-178 ppm, $\text{C}=\text{O}$ carbon was seen at 166-170 ppm for compounds (**4a-h**).

Tetra-2-acetyl-amino-4-acetyl-4,5-dihydro-1,3,4-thiodiazol compounds (**5a,b,c,e,f,g**) were obtained form the reaction tetra-thiosemicarbazone derivatives (**3a-h**) with acetic anhydride (Scheme 4).



Scheme 4

In the IR spectral data of (**5a,b,c,e,f,g**) compounds, two sharp carbonyl peaks were observed. This showed that the acetyl group connected thiosemicarbazones at the two position. Carbonyl groups stretching frequency corresponded to esteric carbonyl stretching and amidic carbonyl stretching. The data was observed at 1640-1678 cm^{-1} . On the other hand, NH stretching frequency which one did not have acetyl group was seen at 3160-3225 cm^{-1} .

In the $^1\text{H-NMR}$ spectral data of compound **5a,b,c,e,f,g**, acetyl group protons were observed 1.99-2.07 ppm and 2.21-2.36 ppm integrating for twelve protons. At the same time CH protone which were bound to the 5-position of the thiadiazole ring were seen at 6.77-7.37 ppm singlet peak integrating for four protons. The $^1\text{H-NMR}$ result show that carbon of azomethyne ($\text{CH}=\text{N}$) converted from sp^2 to sp^3 hybridize carbon. In the $^1\text{H-NMR}$ spectral data of compounds **5a-c**, NH protons were seen at 11.47-11.80 ppm singlet peak integrating for four protons (exchangeable with D_2O).

In the $^{13}\text{C-NMR}$ spectral data of compound **5a,b,c,e,f,g**, the CH_3 of acetyl groups carbon was seen 21.68-22.53 ppm and 23.21-23.37 ppm. The data was the most important evidence for acetyl group connecting two different position. The CH carbon peak which was bound to the 5-position of the thiadiazole ring was seen at 63-66 ppm in the $^{13}\text{C-NMR}$. Another sp^2 hybridized carbon peak belonging to the thiadiazole ring was seen at 146.01-150.54 ppm. The other important data for the acetyl group connecting two different positions was $\text{C}=\text{O}$ group carbon peak which was seen at 167-169 and 169-171 ppm. The data is consistent with literature⁶³

Experimental Section

General Procedures. Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$ 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 was carried out on a C,H,N-O rapid elemental analyzer Hewlett-Packard 185 for C, H and N and results are within 0.4 % of the theoretical values. The MS spectra were measured with an Micromass Quattro LC/ULTIMA LC-MS/MS spectrometer equipped with pyridine-methanol as solvent. All experiments were performed in the positive ion mode. All the chemicals were obtained from Fluka Chemie AG Buchi (Switzerland). Compound 1 was synthesized using the published methods.⁵⁶ Compound 2c is published at Acta Crystallographica.⁵⁷

General method for the synthesis tetra-aldehydes and tetra-ketones (2)

To a solution of hydroxy aldehyde and keton derivatives (100 mmol) in absolute ethanol (50 ml) were added KOH (5.6 g, 100 mmol) and tetra-*o*-methyl-tetra-bromide (10.0 g, 25 mmol). After the mixture was refluxed and stirred for 20 hours, the solution was filtered and the solid obtained was washed with ethyl alcohol and ether. The precipitate formed was recrystallized from appropriate solvent to afford the desired compound.

6'-(2-(1,3-Bis(4-bromo-2-formylphenoxy)propan-2-ylidene)propane-1,3-diyl)bis-(oxy)bis(3-bromo benzaldehyde) (2a). The solid obtained was washed with H_2O and recrystallized from DMF/ethyl alcohol (1:2), (yield:86 %); m.p. 242-243 °C; IR (KBr) (ν , cm^{-1}), 3065 (Ar-CH), 2733-2752 (CHO), 1678-1702 (C=O); $^1\text{H-NMR}$ (DMSO-d_6) δ (ppm) 5.16 (s, 8H, O-CH₂), 7.30-7.35 (d, 4H, ar-H), 7.65-7.66 (d, 4H, ar-H), 7.79-7.80 and 7.77-7.76 (dd, 4H, ar-H), 10.02 (s, 4H, CHO); $^{13}\text{C-NMR}$ (DMSO-d_6) δ (ppm) 65.90 (O-CH₂), ar-C: [112.75 (C), 116.68 (CH), 125.91 (C), 129.72 (CH), 138.13 (CH), 159.31 (C)], 134.76 (C=C), 187.60 (C=O); MS(ESI-*m/z*): ($\text{M}+1$)⁺: 881.55; Analysis (% Calculated/found) for $\text{C}_{34}\text{H}_{24}\text{Br}_4\text{O}_8$ (Mw 880.17) C: 46.40/46.48, H: 2.75/2.71

4,4'-(2-(1,3-Bis(4-formyl-2-methoxyphenoxy)propan-2-ylidene)propane-1,3-diyl)bis(oxy)bis(3-methoxybenzaldehyde) (2b). The solid obtained was washed with H_2O and recrystallized from DMF/ethyl alcohol (1:2) (yield: 82 %); m.p. 238-239 °C; IR (KBr) (ν , cm^{-1}), 3081 (Ar-CH), 2724-2747 (CHO), 1686 (C=O); $^1\text{H-NMR}$ (DMSO-d_6) δ (ppm) 3.67 (s, 12H, OCH₃), 4.98 (s, 8H, O-CH₂), 7.30-7.31 (d, 4H, ar-H), 7.25-7.29 (d, 4H, ar-H), 7.47-7.50 (d, 4H, ar-H), 9.81 (s, 4H, CHO); $^{13}\text{C-NMR}$ (DMSO-d_6) δ (ppm) 55.31 (OCH₃), 65.53 (O-CH₂), ar-C: [109.36 (CH), 112.90 (CH), 125.71 (CH), 129.90 (C), 149.28 (C), 152.89 (C)], 134.87 (C=C), 191.40 (C=O). MS(ESI-*m/z*): ($\text{M}+1$)⁺: 685.13; Analysis (% Calculated/found) for $\text{C}_{38}\text{H}_{36}\text{O}_{12}$ (Mw 684.69) C: 66.66/66.72, H: 5.30/5.34

1,1'-(4,4'-(2-(1,3-Bis(4-acetylphenoxy)propan-2-ylidene)propane-1,3-diyl) bis(oxy)bis(4,1-phenylene))diethanone (2d). The solid obtained was washed with H_2O and recrystallized from acetone/chloroform (1:1) yield: 11.34 g (73 %); m.p. 167 °C; IR (KBr) (ν , cm^{-1}), 3045 (Ar-CH),

1674 (C=O); $^1\text{H-NMR}$ (DMSO- d_6) δ (ppm) 2.51 (s, 12H, CH₃), 4.99 (s, 8H, O-CH₂), 7.04-7.09 (d, 8H, ar-H), 7.88-7.92 (d, 8H, ar-H); $^{13}\text{C-NMR}$ (DMSO- d_6) δ (ppm) 26.35 (CH₃), 64.90 (O-CH₂), ar-C: [114.50 (CH), 130.07 (C), 100.29 (CH), 161.99 (C)], 135.05 (C=C), 196.24 (C=O); MS(ESI- m/z): (M+1)⁺: 621.34; Analysis (% Calculated/found) for C₃₈H₃₆O₈ (Mw 620.24) C: 73.53/73.49, H: 5.85/5.93

General method for the synthesis tetra-thiosemicarbazone (3)

Compounds **2a-d** (2.5 mmol) and thiosemicarbazite or 4-methyl thiosemicarbazite (10 mmol) were refluxed at 160°C for 4 hours in oil bath with stirring. To reaction content DMF was added and dissolved. Then water was added to solution and 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.

(2Z,2'E)-2,2'-(6,6'-(2-(1,3-Bis(4-bromo-2-((E)-(2-carbamothioylhydrazono)methyl)phenoxy)propan-2-ylidene)propane-1,3-diyl)bis(oxy)bis(3-bromo-6,1-phenylene))bis(methan-1-yl-1-ylidene)bis(hydrazinecarbothioamide) (3a). The solid obtained was washed with H₂O and recrystallized from DMF/ethyl alcohol/water (1:2:1), yield: 2.14 g (73 %); m.p. 263 °C; IR (KBr) (ν , cm⁻¹), 3258-3358 (NH₂), 3151 (NH), 3005 (Ar-CH), 1590 (C=N); $^1\text{H-NMR}$ (DMSO- d_6) δ (ppm) 5.13 (s, 8H, O-CH₂), 7.16-7.20 (d, 4H, ar-H), 7.48-7.51 (d, 4H, ar-H), 8.29 (bs, 16H, ar-H, CH=N, NH₂), 11.39 (s, 4H, NH); $^{13}\text{C-NMR}$ (DMSO- d_6) δ (ppm) 64.96 (O-CH₂), ar-C: [113.33 (C), 115.45 (CH), 124.58 (C), 127.90 (CH), 135.95 (CH), 155.61 (C)], 133.92 (C=C), 132.97 (CH=N), 177.65 (C=S); MS(ESI- m/z): (M)⁺: 1172.60; Analysis (% Calculated/found) for C₃₈H₃₆Br₄N₁₂O₄S₄ (Mw 1172.64) C: 38.92/38.87, H: 3.09/3.14, N:4.33/4.31

(2Z,2'E)-2,2'-(4,4'-((E)-2-(1-(4-((E)-(2-Carbamothioylhydrazono)methyl)-2-methoxyphenoxy)-3-(4-((Z)-(2-carbamothioylhydrazono)methyl)-2-methoxyphenoxy)propan-2-ylidene)propane-1,3-diyl)bis(oxy)bis(3-methoxy-4,1-phenylene))bis(methan-1-yl-1-ylidene)bis(hydrazinecarbothioamide) (3b).

The solid obtained was washed with H₂O and recrystallized from DMF/ethyl alcohol/water (1:2:1), yield: 1.54 g (63 %); m.p. 207-209 °C; IR (KBr) (ν , cm⁻¹), 3269-3316 (NH₂), 3159 (NH), 3012 (Ar-CH), 1598 (C=N); $^1\text{H-NMR}$ (DMSO- d_6) δ (ppm) 3.75 (s, 12H, OCH₃), 4.89 (s, 8H, O-CH₂), 7.13 (s, 8H, ar-H), 7.52 (s, 4H, ar-H), 7.99 (s, 4H, CH=N), 8.20 (s, 8H, NH₂), 11.36 (s, 4H, NH); $^{13}\text{C-NMR}$ (DMSO- d_6) δ (ppm) 55.58 (OCH₃), 65.38 (O-CH₂), ar-C: [108.66 (CH), 113.47 (CH), 121.89 (CH), 127.55 (C), 149.40 (C), 149.50 (C)], 135.16 (C=C), 142.30 (CH=N), 177.39 (C=S); MS(ESI- m/z): (M+1)⁺: 978.74; Analysis (% Calculated/found) for C₄₂H₄₈N₁₂O₈S₄ (Mw 977.17) C: 51.62/51.65, H: 4.95/4.92, N: 17.20/17.26

(2Z,2'E)-2,2'-(2,2'-((2E)-2-(1-(1-((2-Carbamothioylhydrazono)methyl) naphthalen-2-yloxy)-3-(1-((E)-(2-carbamothioylhydrazono)methyl)naphthalen-2-yloxy)propan-2-ylidene)propane-1,3-diyl)bis(oxy)bis(naphthalene-2,1-diyl))bis(methan-1-yl-1-ylidene)bis(hydrazinecarbothioamide) (3c). The solid obtained was washed with H₂O and recrystallized from DMF/ethyl alcohol/water (1:2:1) yield: 2.17 g, (82 %); m.p. 201-202 °C; IR

(KBr) (ν , cm^{-1}), 3253-3324 (NH_2), 3151 (NH), 3049 (Ar-CH), 1589 (C=N); $^1\text{H-NMR}$ (DMSO- d_6) δ (ppm) 5.44 (s, 8H, O- CH_2), 7.45-8.01 (m, 20H, ar-H), 8.85 (s, 4H, ar-H), 8.85 (s, 4H, CH=N), 8.28 (s, 8H, NH_2), 11.59 (s, 4H, NH); $^{13}\text{C-NMR}$ (DMSO- d_6) δ (ppm) 65.66 (O- CH_2), ar-C: [114.38 (C), 114.68 (CH), 123.99 (CH), 125.91 (CH), 128.01 (CH), 128.28 (CH), 128.70 (C), 130.35 (CH), 132.38 (C), 156.80 (C)], 134.39 (C=C), 140.94 (CH=N), 177.38 (C=S); MS(ESI- m/z): (M) $^+$: 1057.08; Analysis (% Calculated/found) for $\text{C}_{54}\text{H}_{48}\text{N}_{12}\text{O}_4\text{S}_4$ (Mw 1057.30) C: 61.34/61.29, H: 4.58/4.61, N: 15.90/15.87

(2Z,2'E)-2,2'-(1,1'-(4,4'-(2-(1,3-Bis(4-((Z)-1-(2-carbamothioylhydrazono)

ethyl)phenoxy)propan-2-ylidene)propane-1,3-diyl)bis(oxy)bis(4,1-phenylene)) bis(ethan-1-yl-1-ylidene))bis(hydrazinecarbo- thioamide) (3d). The solid obtained was washed with H_2O and recrystallized from DMF/ethyl alcohol/water (1:2:1), yield: 1.92 g (63 %); m.p. 98 °C; IR (KBr) (ν , cm^{-1}), 3137-3255(NH_2), 3148 (NH), 3058 (Ar-CH), 1599 (C=N); $^1\text{H-NMR}$ (DMSO- d_6) δ (ppm) 2.23 (s, 12H, CH_3), 4.90 (s, 8H, O- CH_2), 6.93-6.97 (d, 8H, ar-H), 7.84-7.88 (d, 8H, ar-H), 7.88 (s, 4H, NH_2), 8.22 (s, 4H, NH_2), 10.13 (s, 4H, NH); $^{13}\text{C-NMR}$ (DMSO- d_6) δ (ppm) 13.76 (CH_3), 64.69 (O- CH_2), ar-C: [114.30 (CH), 128.01 (C), 130.35 (CH), 159.19 (C)], 135.14 (C=C), 147.60 (CH=N), 178.43 (C=S); MS(ESI- m/z): ($\text{M}+\text{K}+1$) $^+$: 953.43; Analysis (% Calculated/found) for $\text{C}_{42}\text{H}_{48}\text{N}_{12}\text{O}_4\text{S}_4$ (Mw 913.17) C: 55.24/55.18, H: 5.30/5.34, N: 18.41/18.43

(2Z,2'E)-2,2'-(6,6'-(2-(1,3-Bis(4-bromo-2-((E)-2-(methylcarbamothioyl)

hydrazono)methyl)phenoxy)propan-2-ylidene)propane-1,3-diyl)bis(oxy)bis(3-bromo-6,1-phenylene))bis(methan-1-yl-1-ylidene)bis(N-methylhydrazine carbothioamide) (3e). The solid obtained was washed with H_2O and recrystallized from DMF/ethyl alcohol (1:2), yield: 2.30 g (75 %); m.p. 234-235 °C; IR (KBr) (ν , cm^{-1}), 3157-3357 (NH), 3059 (Ar-CH), 1589 (C=N); $^1\text{H-NMR}$ (DMSO- d_6) δ (ppm) 3.00-3.02 (d, 12H, NCH_3), 5.14 (s, 8H, O- CH_2), 7.15-7.20 (d, 4H, ar-H), 7.45-7.50 (d, 4H, ar-H), 8.17 (s, 4H, ar-H), 8.22 (s, 4H, CH=N), 8.55-8.57 (d, 4H, NH-CH_3), 11.39 (s, 4H, NH); $^{13}\text{C-NMR}$ (DMSO- d_6) δ (ppm) 30.72 (NCH_3), 65.00 (O- CH_2), ar-C: [113.193 (C), 115.54 (CH), 124.59 (C), 127.53 (CH), 135.36 (CH), 155.61 (C)], 133.74 (C=C), 132.86 (CH=N), 177.28 (C=S); MS(ESI- m/z): ($\text{M}+1$) $^+$: 1229.98; Analysis (% Calculated/found) for $\text{C}_{42}\text{H}_{44}\text{Br}_4\text{N}_{12}\text{O}_4\text{S}_4$ (Mw 1228.74) C: 41.05/41.07, H: 3.61/3.65, N: 13.68/13.62

(2Z,2'E)-2,2'-(4,4'-((E)-2-(1-(2-Methoxy-4-((E)-2-(methylcarbamothioyl)

hydrazono)methyl)phenoxy)-3-(2-methoxy-4-((Z)-2-(methylcarbamothioyl)

hydrazono)methyl)phenoxy)propan-2-ylidene)propane-1,3-diyl)bis(oxy)bis(3-methoxy-4,1-phenylene))bis(methan-1-yl-1-ylidene)bis(N-methylhydrazine carbothioamide) (3f). The solid obtained was washed with H_2O and recrystallized from DMF/ethyl alcohol/water (1:2:1), yield: 1.59 g (63 %); m.p. 178-179 °C; IR (KBr) (ν , cm^{-1}), 3186-3368 (NH), 3067 (Ar-CH), 1599 (C=N); $^1\text{H-NMR}$ (DMSO- d_6) δ (ppm) 3.02-3.04 (d, 12H, NCH_3), 3.76 (s, 12H, OCH_3), 4.89 (s, 8H, O- CH_2), 7.09-7.52 (m, 8H, ar-H), 7.45 (s, 4H, ar-H), 7.98 (s, 4H, CH=N), 8.43-8.45 (d, 4H, NH-CH_3), 11.42 (s, 4H, NH); $^{13}\text{C-NMR}$ (DMSO- d_6) δ (ppm) 30.74 (NCH_3), 55.64 (OCH_3), 65.46 (O- CH_2), ar-C: [109.16 (CH), 113.64 (CH), 121.48 (CH), 127.59 (C), 149.38 (C), 149.44 (C)], 135.16 (C=C), 141.82 (CH=N), 177.31 (C=S); MS(ESI- m/z): (M) $^+$: 1033.38;

Analysis (% Calculated/found) for $C_{46}H_{56}N_{12}O_8S_4$ (Mw 1033.26) C: 53.47/53.42, H: 5.46/5.43, N: 16.27/16.31

(2Z,2'E)-2,2'-(2,2'-((2E)-2-(1-(1-((2-(Methylcarbamothioyl)hydrazono) methyl)naphthalen-2-yloxy)-3-(1-((E)-(2-(methylcarbamothioyl)hydrazono) methyl)naphthalen-2-yloxy)propan-2-ylidene)propane-1,3-diyl)bis(oxy)bis (naphthalene-2,1-diyl))bis(methan-1-yl-1-ylidene)bis(N-methylhydrazine carbothioamide) (3g). The solid obtained was washed with H_2O and recrystallized from DMF/ethyl alcohol (1:2) yield: 1.75 g (63 %); m.p. 238-239 °C; IR (KBr) (ν , cm^{-1}), 3152-3373 (NH), 3049 (Ar-CH), 1622 (C=N); 1H -NMR (DMSO- d_6) δ (ppm) 3.04-3.06 (d, 12H, NCH₃), 5.45 (s, 8H, O-CH₂), 7.36-7.43 (t, 4H, ar-H), 7.49-7.57 (t, 4H, ar-H), 7.82-7.86 (d, 4H, ar-H), 8.00-8.04 (d, 4H, ar-H), 8.81-8.85 (d, 4H, ar-H), 8.81 (s, 4H, CH=N), 8.81-8.84 (d, 4H, NH-CH₃), 11.60 (s, 4H, NH); ^{13}C -NMR (DMSO- d_6) δ (ppm) 31.04 (NCH₃), 65.56 (O-CH₂), ar-C: [114.39 (C), 114.55 (CH), 123.91 (CH), 125.50 (CH), 127.99 (CH), 128.21 (CH), 128.69 (C), 130.40 (CH), 132.07 (C), 156.54 (C)], 134.40 (C=C), 140.36 (CH=N), 177.32 (C=S); MS(ESI- m/z): (M)⁺ : 1113.33; Analysis (% Calculated/found) for $C_{58}H_{56}N_{12}O_4S_4$ (Mw 1113.40) C: 62.57/62.62, H: 5.07/5.01, N: 15.10/15.06

(2Z,2'E)-2,2'-(1,1'(4,4'-(2-(1,3-Bis(4-((Z)-1-(2-methylcarbamothioyl)hydrazono)ethyl)phenoxy)propan-2-ylidene)propane-1,3-diyl)bis(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 from DMF/ethyl alcohol (1:2), yield: 1.19 g (49 %); m.p. 115 °C; IR (KBr) (ν , cm^{-1}), 3162-3357 (NH), 3038 (Ar-CH), 1599 (C=N); 1H -NMR (DMSO- d_6) δ (ppm) 2.26 (s, 12H, CH₃), 3.02-3.04 (d, 12H, NCH₃), 4.93 (s, 8H, O-CH₂), 6.97-7.01 (d, 8H, ar-H), 7.86-7.90 (d, 8H, ar-H), 8.40-8.43 (d, 4H, NH-CH₃), 10.16 (s, 4H, NH); ^{13}C -NMR (DMSO- d_6) δ (ppm) 13.78 (CH₃), 30.95 (NCH₃), 64.78 (O-CH₂), ar-C: [114.30 (CH), 127.97 (C), 130.44 (CH), 159.17 (C)], 135.20 (C=C), 147.30 (CH=N), 178.35 (C=S); MS(ESI- m/z): (M+1)⁺: 969.51; Analysis (% Calculated/found) for $C_{46}H_{56}N_{12}O_4S_4$ (Mw 968.34) C: 57.00/57.02, H: 5.82/5.78, N: 17.34/17.35

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

To a solution of compounds **3a-h** (5 mmol) in absolute ethanol (60 ml) were added ethyl-2-chloro-acetoacetate (0.287 ml, 20 mmol). After the mixture was refluxed and stirred for 80 hours, the solution was filtered and the solid obtained was washed ethyl alcohol and deionized water. The precipitated solid was recrystallized from appropriate solvent to afford the desired compound.

(2Z,2'Z)-Diethyl 2,2'-((2Z,2'Z)-(6,6'-((Z)-2,3-bis((4-bromo-2-((E)-((Z)-(5-(ethoxy-carbonyl)-4-methylthiazol-2(3H)-ylidene)hydrazono)methyl)phenoxy)methyl)-but-2-ene-1,4-diyl)bis(oxy)bis(3-bromo-6,1-phenylene))bis(methan-1-yl-1-ylidene)bis(hydrazine-2,1-diylidene))bis(4-methyl-2,3-dihydrothiazole-5-carboxylate) (4a). The solid obtained was washed with H_2O and recrystallized from DMF/ethyl acetate/ethyl alcohol (1:1:2), yield: 0.45 g (55 %); m.p. 289-290 °C; IR (KBr) (ν , cm^{-1}), 3165 (NH), 3045 (Ar-CH), 1697 (C=O), 1592 (C=N), 1092 (OCH₂CH₃); 1H -NMR (DMSO- d_6) δ (ppm) 1.27 (s, 12H, OCH₂CH₃), 2.47 (s,

12H, thiazole CH₃), 4.18-4.22 (d, 8H, OCH₂CH₃), 5.08 (s, 8H, O-CH₂), 7.15-7.19 (d, 4H, ar-H), 7.42-7.46 (d, 4H, ar-H), 7.73 (s, 4H, ar-H), 8.12 (s, 4H, CH=N), 12.29 (s, 4H, NH); ¹³C-NMR (DMSO-d₆) δ (ppm) 14.23 (OCH₂CH₃), 17.06 (thiazole CH₃), 60.02 (OCH₂CH₃), 65.53 (O-CH₂), ar-C: [113.15 (C), 115.98 (CH), 124.66 (C), 126.93 (CH), 132.92 (CH), 155.22 (C)], thiazole C: [109.25 (C), 158.09 (C), 161.79 (C)], 134.52 (C=C), 137.67 (CH=N), 168.79 (C=O); MS(ESI-*m/z*): (M+1)⁺: 1628.00; Analysis (% Calculated/found) for C₆₃H₆₂Br₄N₁₂O₁₂S₄ (Mw 1627.12) C: 46.50/46.45, H: 3.84/3.87, N: 10.33/10.36

(2Z,2'Z)-Diethyl 2,2'-((2Z,2'Z)-(4,4'-((E)-2,3-bis((4-((E)-((Z)-(5-(ethoxy carbonyl)-4-methylthiazol-2(3H)-ylidene)hydrazono)methyl)-2-methoxyphenoxy) methyl)-but-2-ene-1,4-diyl)bis(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 H₂O and recrystallized from DMF/*n*-butylacetate/ethyl alcohol (1:1:2), yield: 0.47 g (67 %); m.p. 249-250 °C; IR (KBr) (ν, cm⁻¹), 3159 (NH), 3054 (Ar-CH), 1669 (C=O), 1593 (C=N), 1091 (OCH₂CH₃); ¹H-NMR (DMSO-d₆) δ (ppm) 1.20-1.27 (t, 12H, OCH₂CH₃), 2.44 (s, 12H, thiazole CH₃), 3.73 (s, 12H, OCH₃), 4.15-4.19 (q, 8H, OCH₂CH₃), 4.87 (s, 8H, O-CH₂), 7.09-7.21 (m, 12H, ar-H), 7.93-7.98 (d, 4H, CH=N), 12.24 (s, 4H, NH); ¹³C-NMR (DMSO-d₆) δ (ppm) 14.25 (OCH₂CH₃), 17.06 (thiazole CH₃), 55.35 (OCH₃), 59.97 (OCH₂CH₃), 65.40 (O-CH₂), ar-C: [108.85 (CH), 113.91 (CH), 120.45 (CH), 127.29 (C), 149.33 (C), 158.13 (C)], thiazole C: [108.59 (C), 161.85 (C), 162.22 (C)], 135.22 (C=C), 144.50 (CH=N), 168.88 (C=O); MS(ESI-*m/z*): (M)⁺: 1417.38; Analysis (% Calculated/found) for C₆₆H₇₂N₁₂O₁₆S₄ (Mw 1417.61) C: 46.50/46.45, H: 3.84/3.87, N: 10.33/10.36

(2Z,2'Z)-Diethyl 2,2'-((2Z,2'Z)-(2,2'-((Z)-2,3-bis((1-((E)-((Z)-(5-(ethoxy carbonyl)-4-methylthiazol-2(3H)-ylidene)hydrazono)methyl)naphthalen-2-yloxy) methyl)but-2-ene-1,4-diyl)bis(oxy)bis(naphthalene-2,1-diyl)bis(methan-1-yl-1-ylidene)bis(hydrazine-2,1-diylidene))bis(4-methyl-2,3-dihydrothiazole-5-carboxylate) (4c). The solid obtained was washed with H₂O and recrystallized from DMF/diethyl ether (1:2), yield: 0.43 g (57 %); m.p. 214-215 °C; IR (KBr) (ν, cm⁻¹), 3049 (Ar-CH), 1697 (C=O), 1594 (C=N), 1088 (OCH₂CH₃); ¹H-NMR (DMSO-d₆) δ (ppm) 1.21-1.28 (t, 12H, OCH₂CH₃), 2.41 (s, 12H, thiazole CH₃), 4.19-4.23 (d, 8H, OCH₂CH₃), 5.42 (s, 8H, O-CH₂), 7.36-7.40 (d, 4H, ar-H), 7.51-7.58 (t, 4H, ar-H), 7.64-7.68 (d, 4H, ar-H), 7.75-7.78 (d, 4H, ar-H), 7.88-7.92 (d, 4H, ar-H), 8.97-9.01 (d, 4H, ar-H), 8.78 (s, 4H, CH=N), 12.41 (s, 4H, NH); ¹³C-NMR (DMSO-d₆) δ (ppm) 14.22 (OCH₂CH₃), 17.17 (thiazole CH₃), 59.94 (OCH₂CH₃), 65.99 (O-CH₂), ar-C: [114.60 (C), 114.82 (CH), 123.97 (CH), 125.02 (CH), 127.85 (CH), 128.39 (CH), 128.56 (C), 130.24 (CH), 132.06 (C), 156.33 (C)], thiazole C: [108.78 (C), 158.42 (C), 161.83 (C)], 134.80 (C=C), 141.89 (CH=N), 168.81 (C=O); MS(ESI-*m/z*): (M+1)⁺: 1498.78 Analysis (% Calculated/found) for C₇₈H₇₂N₁₂O₁₂S₄ (Mw 1497.74) C: 62.55/62.49, H: 4.85/4.89, N: 11.22/11.25

(2Z,2'Z)-Diethyl 2,2'-((2Z,2'Z)-(1,1'-(4,4'-((2-(1-(4-((E)-1-((Z)-(5-(ethoxy carbonyl)-4-methylthiazol-2(3H)-ylidene)hydrazono)ethyl)phenoxy)-3-(4-((Z)-1-((Z)-(5-(ethoxycarbonyl)-4-methylthiazol-2(3H)-ylidene)hydrazono)ethyl) phenoxy)propan-2-ylidene)propane-1,3-diyl)bis(oxy)bis(4,1-phenylene))bis (ethan-1-yl-1-

ylidene))bis(hydrazine-2,1-diylidene))bis(4-methyl-2,3-dihydro thiazole-5-carboxylate) (4d).

The solid obtained was washed with H₂O and recrystallized from chloroform/petroleum ether (1:2), yield: 0.36 g (52 %); m.p. 155 °C; IR (KBr) (ν, cm⁻¹), 3052 (Ar-CH), 1696 (C=O), 1601 (C=N), 1093 (OCH₂CH₃); ¹H-NMR (CDCl₃-d₆) δ (ppm) 1.33-1.40 (t, 12H, OCH₂CH₃), 2.37 (s, 12H, CH₃), 2.55 (s, 12H, thiazole CH₃), 4.25-4.36 (q, 8H, OCH₂CH₃), 4.90 (s, 8H, O-CH₂), 6.97-7.03 (d, 8H, ar-H), 7.90-7.94 (d, 8H, ar-H), 11.76 (s, 4H, NH); ¹³C-NMR (DMSO-d₆) δ (ppm) 13.99 (CH₃), 14.55 (OCH₂CH₃), 17.49 (thiazole CH₃), 60.57 (OCH₂CH₃), 65.94 (O-CH₂), ar-C: [114.12 (CH), 127.35 (C), 130.16 (CH), 156.84 (C)], 135.29 (C=C), 147.89 (CH=N), 168.22 (C=O); MS(ESI-*m/z*): (M)⁺: 1353.64; Analysis (% Calculated/found) for C₆₆H₇₂N₁₂O₁₂S₄ (Mw 1353.6) C: 55.56/55.54, H: 5.36/5.31, N: 12.42/12.47

(2Z,2'Z)-Diethyl 2,2'-((2Z,2'Z)-(6,6'-((Z)-2,3-bis((4-bromo-2-((E)-((Z)-(5-(ethoxy carbonyl)-3,4-dimethylthiazol-2(3H)-ylidene)hydrazono)methyl)phenoxy) methyl)but-2-ene-1,4-diyl)bis(oxy)bis(3-bromo-6,1-phenylene))bis(methan-1-yl-1-ylidene)bis(hydrazine-2,1-diylidene))bis(3,4-dimethyl-2,3-dihydrothiazole-5-carboxylate) (4e).

The solid obtained was washed with H₂O and recrystallized from DMSO, yield: 0.52 g (62 %); m.p. 279-280 °C; IR (KBr) (ν, cm⁻¹), 3032 (Ar-CH), 1699 (C=O), 1600 (C=N), 1088 (OCH₂CH₃); ¹H-NMR (CDCl₃-d₆) δ (ppm) 1.33-1.39 (t, 12H, OCH₂CH₃), 2.57 (s, 12H, thiazole CH₃), 3.43 (s, 12H, N-CH₃), 4.27-4.30 (q, 8H, OCH₂CH₃), 4.82 (s, 8H, O-CH₂), 6.78-6.81 (d, 4H, ar-H), 7.36-7.39 (d, 4H, ar-H), 8.09 (s, 4H, ar-H), 8.45 (s, 4H, CH=N); ¹³C-NMR (CDCl₃-d₆) δ (ppm) 12.87 (OCH₂CH₃), 14.44 (thiazole CH₃), 31.73 (N-CH₃), 60.86 (OCH₂CH₃), 65.71 (O-CH₂), ar-C: [113.99 (C), 114.15 (CH), 126.27 (C), 128.32 (CH), 129.51 (CH), 155.94 (C)], thiazole C: [103.92 (C), 146.75 (C), 162.17 (C)], 133.23 (C=C), 147.42 (CH=N), 168.39 (C=O); MS(ESI-*m/z*): (M)⁺: 1683.62; Analysis (% Calculated/found) for C₆₇H₇₀Br₄N₁₂O₁₂S₄ (Mw 1683.23) C: 47.81/47.78, H: 4.19/4.23, N: 9.99/10.07

(2Z,2'Z)-Diethyl 2,2'-((2Z,2'Z)-(4,4'-((E)-2,3-bis((4-((E)-((Z)-(5-(ethoxy carbonyl) -3,4-dimethylthiazol-2(3H)-ylidene)hydrazono)methyl)-2-methoxy phenoxy) methyl)but-2-ene-1,4-diyl)bis(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 H₂O and recrystallized from DMF/*n*-butylacetate (1:2), yield: 0.45 g (61 %); m.p. 195 °C; IR (KBr) (ν, cm⁻¹), 3048 (Ar-CH), 1669 (C=O), 1600 (C=N), 1084 (OCH₂CH₃); ¹H-NMR (DMSO-d₆) δ (ppm) 1.21-1.28 (t, 12H, OCH₂CH₃), 2.52 (s, 12H, thiazole CH₃), 3.39 (s, 12H, N-CH₃), 3.58 (s, 12H, OCH₃), 4.17-4.21 (q, 8H, OCH₂CH₃), 4.91 (s, 8H, O-CH₂), 7.16-7.31 (m, 12H, ar-H), 8.25 (s, 4H, CH=N); ¹³C-NMR (DMSO-d₆) δ (ppm) 12.52 (OCH₂CH₃), 14.15 (thiazole CH₃), 31.37 (N-CH₃), 55.32 (OCH₃), 60.28 (OCH₂CH₃), 65.35 (O-CH₂), ar-C: [109.35 (CH), 113.90 (CH), 121.02 (CH), 128.26 (C), 149.26 (C), 152.58 (C)], thiazole C: [100.99 (C), 161.33 (C), 165.62 (C)], 135.33 (C=C), 148.27 (CH=N), 170.78 (C=O); MS(ESI-*m/z*): (M)⁺: 1473.61; Analysis (% Calculated/found) for C₇₀H₈₀N₁₂O₁₆S₄ (Mw 1473.72) C: 57.05/57.11, H: 5.47/5.43, N: 11.41/11.38

(2Z,2'Z)-Diethyl 2,2'-((2Z,2'Z)-(2,2'-((Z)-2,3-bis((1-((E)-((Z)-(5-(ethoxy carbonyl) -3,4-dimethylthiazol-2(3H)-ylidene)hydrazono)methyl)naphthalen-2-yloxy) methyl)but-2-ene-

1,4-diyl)bis(oxy)bis (naphthalene-2,1-diyl))bis(methan-1-yl-1-ylidene)bis(hydrazine-2,1-diylidene))bis(3,4-dimethyl-2,3-dihydrothiazole-5-carboxylate) (4g). The solid obtained was washed with H₂O and recrystallized from DMF/diethyl ether (1:2), yield: 0.35 g (45 %); m.p. 214-215 °C; IR (KBr) (ν , cm⁻¹), 3181 (-NH-), 3049 (Ar-CH), 1693 (C=O), 1588 (C=N), 1093 (OCH₂CH₃); ¹H-NMR (DMSO-d₆) δ (ppm) 1.24-1.30 (t, 12H, OCH₂CH₃), 2.48 (s, 12H, thiazole CH₃), 3.10 (s, 12H, N-CH₃), 4.13-4.23 (q, 8H, OCH₂CH₃), 5.25 (s, 8H, O-CH₂), 7.34-7.41 (t, 4H, ar-H), 7.49-7.58 (t, 8H, ar-H), 7.78-7.90 (m, 8H, ar-H), 9.13-9.23 (d, 4H, ar-H), 8.99 (s, 4H, CH=N); ¹³C-NMR (DMSO-d₆) δ (ppm) 14.25 (OCH₂CH₃), 14.11 (thiazole CH₃), 31.17 (N-CH₃), 60.27 (OCH₂CH₃), 66.61 (O-CH₂), ar-C: [114.82 (C), 115.83 (CH), 123.92 (CH), 125.83 (CH), 127.62 (CH), 128.23 (CH), 128.93 (C), 130.81 (CH), 131.92 (C), 150.32 (C)], thiazole C: [100.93 (C), 156.23 (C), 165.34 (C)], 135.48 (C=C), 148.00 (CH=N), 165.34 (C=O); MS(ESI-*m/z*): (M)⁺: 1553.81; Analysis (% Calculated/found) for C₈₂H₈₀N₁₂O₁₂S₄ (Mw 1553.85) C: 63.38/63.32, H: 5.19/5.23, N: 10.82/10.87

(2Z,2'Z)-Diethyl 2,2'-((2Z,2'Z)-(1,1'-(4,4'-(2-(1-(4-((E)-1-((Z)-(5-(ethoxy carbonyl)-3,4-dimethyl thiazol-2(3H)-ylidene)hydrazono)ethyl)phenoxy)-3-(4-((Z)-1-((Z)-(5-(ethoxycarbonyl)-3,4-dimethylthiazol-2(3H)-ylidene)hydrazono) ethyl)phenoxy)propan-2-ylidene)propane-1,3-diyl)bis(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 H₂O and recrystallized from chloroform/petroleum ether (1:2), yield: 0.31 g (44 %); m.p. 155 °C; IR (KBr) (ν , cm⁻¹), 3037 (Ar-CH), 1698 (C=O), 1597 (C=N), 1092, (OCH₂CH₃); ¹H-NMR (DMSO-d₆) δ (ppm) 1.29-1.38 (t, 12H, OCH₂CH₃), 2.42 (s, 12H, CH₃), 2.58 (s, 12H, thiazole CH₃), 3.48 (s, 12H, N-CH₃), 4.22-4.29 (q, 8H, OCH₂CH₃), 4.88 (s, 8H, O-CH₂), 6.94-6.97 (d, 8H, ar-H), 7.83-7.87 (d, 8H, ar-H); ¹³C-NMR (DMSO-d₆) δ (ppm) 13.05 (CH₃), 14.55 (OCH₂CH₃), 14.65 (thiazole CH₃), 31.68 (N-CH₃), 60.90 (OCH₂CH₃), 65.16 (O-CH₂), ar-C: [114.51 (CH), 128.11 (C), 130.89 (CH), 157.24 (C)], 135.97 (C=C), 147.03 (CH=N), 165.46 (C=O); MS(ESI-*m/z*): (M)⁺: 1409.76; Analysis (% Calculated/found) for C₇₀H₈₀N₁₂O₁₂S₄ (Mw 1409.72) C: 59.64/59.59, H: 5.72/5.76, N: 11.92/11.95

General method for the synthesis tetra-5-acetamido-3-acetyl-2,3-dihydro-1,3,4-thiadiazol-2-yl (5)

Compounds **3a-h** (4 mmol) and acetic acid (10 ml) were refluxed for 20 hours with stirring. Then this solution was poured into ice-water mixture and stirred for 3 hours. The solution was filtered and the solid obtained was washed diethyl ether. The precipitated solid was recrystallized from appropriate solvent to afford the desired compound.

N,N'-(5,5'-(6,6'-(2-(1,3-Bis(2-(5-acetamido-3-acetyl-2,3-dihydro-1,3,4-thiadiazol-2-yl)-4-bromophenoxy)propan-2-ylidene)propane-1,3-diyl)bis(oxy)bis (3-bromo-6,1-phenylene))bis(4-acetyl-4,5-dihydro-1,3,4-thiadiazole-5,2-diyl)) diacetamide (5a). The solid obtained was washed with H₂O and recrystallized from dichloromethane/petroleum ether (1:2), yield: 0.27 g (44 %); m.p. 221-222 °C; IR (KBr) (ν , cm⁻¹), 3224 (NH), 3067 (Ar-CH),

1681,1640 (C=O); ¹H-NMR (DMSO-d₆) δ (ppm) 1.99 (s, 12H, CH₃), 2.22 (s, 12H, CH₃), 5.05 (s, 8H, OCH₂), 6.77 (s, 4H, thiadiazole), 6.90 (s, 4H, ar-H), 7.12-7.16 (d, 4H, ar-H), 7.39-7.43 (d, 4H, ar-H), 11.72 (s, 4H, NH); ¹³C-NMR (DMSO-d₆) δ (ppm) 21.68 (CH₃), 22.04 (CH₃), 65.25 (O-CH₂), ar-C: [112.36 (C), 114.99 (CH), 126.30 (C), 130.86 (CH), 131.78 (CH), 152.94 (C)], thiadiazole C: [61.03 (CH), 146.93 (C)], 135.56 (C=C), 167.56 (C=O), 169.27 (C=O); MS(ESI-*m/z*): (M+1)⁺: 1509.30; Analysis (% Calculated/found) for C₅₄H₅₂Br₄N₁₂O₁₂S₄ (Mw 1508.94) C: 42.98/42.94, H: 3.47/3.51, N: 11.14/11.15

***N,N'*-(5,5'-(4,4'-(2,3-Bis((4-(5-acetamido-3-acetyl-2,3-dihydro-1,3,4-thiadiazol-2-yl)-2-methoxyphenoxy)methyl)but-2-ene-1,4-diy))bis(oxy)bis(3-methoxy-4,1-phenylene))bis(4-acetyl-4,5-dihydro-1,3,4-thiadiazole-5,2-diyl)) diacetamide (5b)**: The solid obtained was washed with H₂O and recrystallized from ethyl alcohol, yield: 0.28 g (52 %); m.p. 180 °C; IR (KBr) (ν, cm⁻¹), 3225 (NH), 3067 (Ar-CH), 1679,1640 (C=O), 1136 (OCH₃); ¹H-NMR (DMSO-d₆) δ (ppm) 2.04 (s, 12H, CH₃), 2.21 (s, 12H, CH₃), 3.64 (s, 12H, OCH₃), 4.76 (s, 8H, OCH₂), 6.87 (s, 4H, thiadiazole), 6.67-6.71 (d, 4H, ar-H), 6.68 (s, 4H, ar-H), 6.99-7.03 (d, 4H, ar-H), 11.76 (s, 4H, NH); ¹³C-NMR (DMSO-d₆) δ (ppm) 21.81 (CH₃), 22.47 (CH₃), 55.34 (OCH₃), 65.44 (O-CH₂), ar-C: [109.17 (CH), 114.11 (CH), 116.74 (CH), 135.72 (C), 147.39 (C), 149.15 (C)], thiadiazole C: [65.65 (CH), 146.01 (C)], 134.59 (C=C), 167.23 (C=O), 169.08 (C=O); MS(ESI-*m/z*): (M+Na)⁺: 1336.55; Analysis (% Calculated/found) for C₅₈H₆₄N₁₂O₁₆S₄ (Mw 1313.46) C: 53.04/52.98, H: 4.91/4.95, N: 12.80/12.83

***N,N'*-(5,5'-(2,2'-(2-(1,3-Bis(1-(5-acetamido-3-acetyl-2,3-dihydro-1,3,4-thiadiazol-2-yl)naphthalen-2-yloxy)propan-2-ylidene)propane-1,3-diy))bis(oxy) bis(naphthalene-2,1-diyl))bis(4-acetyl-4,5-dihydro-1,3,4-thiadiazole-5,2-diyl)) diacetamide (5c)**. The solid obtained was washed with H₂O and recrystallized from ethyl alcohol, yield: 0.31 g (55 %), m.p. 207 °C; IR (KBr) (ν, cm⁻¹), 3160 (NH), 3056 (Ar-CH), 1687,1648 (C=O); ¹H-NMR (DMSO-d₆) δ (ppm) 2.07 (s, 12H, CH₃), 2.36 (s, 12H, CH₃), 5.23 (s, 8H, OCH₂), 7.37 (m, 4H, thiadiazole), 7.41-7.96 (m, 24H, ar-H), 11.80(s, 4H, NH); ¹³C-NMR (DMSO-d₆) δ (ppm) 21.97 (CH₃), 22.60 (CH₃), 67.83 (O-CH₂), ar-C: [113.70 (C), 115.05 (CH), 119.72 (CH), 122.55 (CH), 124.93 (CH), 125.73 (CH), 127.37 (C), 129.16 (CH), 131.40 (C), 147.04 (C)], 134.11 (C=C), 169.19 (C=O), 170.38 (C=O); MS(ESI-*m/z*): (M+1)⁺: 1394.71; Analysis (% Calculated/found) for C₇₀H₆₄N₁₂O₁₂S₄ (Mw 1393.61) C: 60.33/60.28, H: 4.63/4.65, N: 12.06/12.11

***N,N'*-(5,5'-(6,6'-(2-(1,3-Bis(2-(3-acetyl-5-(*N*-methylacetamido)-2,3-dihydro -1,3,4-thiadiazol-2-yl)-4-bromophenoxy)propan-2-ylidene)propane-1,3-diy))bis (oxy)bis(3-bromo-6,1-phenylene))bis(4-acetyl-4,5-dihydro-1,3,4-thiadiazole-5,2-diyl))bis(*N*-methylacetamide) (5e)**. The solid obtained was washed with H₂O and recrystallized from dichloromethane/petroleum ether (1:2), yield: 0.52 g (84 %); m.p. 178-179 °C; IR (KBr) (ν, cm⁻¹), 3066 (Ar-CH), 1678-1661 (C=O); ¹H-NMR (DMSO-d₆) δ (ppm) 2.27 (s, 12H, CH₃), 2.36 (s, 12H, CH₃), 3.44 (s, 12H, N-CH₃), 4.96 (s, 8H, OCH₂), 6.97-6.99 (m, 4H, thiadiazole), 6.94-7.27 (m, 8H, ar-H), 7.32 (m, 4H, ar-H); ¹³C-NMR (DMSO-d₆) δ (ppm) 21.96 (CH₃), 23.03 (CH₃), 35.51 (N-CH₃), 65.87 (O-CH₂), ar-C: [113.66 (C), 114.32 (CH), 126.91 (C), 130.43 (CH), 132.21 (CH), 153.28 (C)], thiadiazole C: [63.08 (CH), 150.54 (C)], 136.88 (C=C), 168.89

(C=O), 170.51 (C=O); MS(ESI-*m/z*): (M+K)⁺: 1605.40; Analysis (% Calculated/found) for C₅₈H₆₀Br₄N₁₂O₁₂S₄ (Mw 1565.05) C: 44.51/44.57, H: 3.86/3.82, N: 10.74/10.68

***N,N'*-(5,5'-(4,4'-(2,3-Bis((4-(3-acetyl-5-(*N*-methylacetamido)-2,3-dihydro-1,3,4-thiadiazol-2-yl)-2-methoxyphenoxy)methyl)but-2-ene-1,4-diyl)bis(oxy)bis(3-methoxy-4,1-phenylene))bis(4-acetyl-4,5-dihydro-1,3,4-thiadiazole-5,2-diyl))bis(*N*-methylacetamide)**

(5f). The solid obtained was washed with H₂O and recrystallized from ethyl alcohol, yield: 0.41 g (74 %); m.p. 165 °C; IR (KBr) (ν, cm⁻¹), 3059 (Ar-CH), 1677-1649 (C=O), 1138 (OCH₃); ¹H-NMR (CDCl₃-d₆) δ (ppm) 2.18 (s, 12H, CH₃), 2.30 (s, 12H, CH₃), 3.48 (s, 12H, N-CH₃), 3.70 (s, 12H, OCH₃), 4.79 (s, 8H, OCH₂), 6.79 (s, 4H, thiadiazole), 6.75-6.86 (m, 12H, ar-H); ¹³C-NMR (CDCl₃-d₆) δ (ppm) 22.12 (CH₃), 23.08 (CH₃), 35.75 (N-CH₃), 55.86 (OCH₃), 68.00 (O-CH₂), ar-C: [109.53 (CH), 114.51 (CH), 117.81 (CH), 135.79 (C), 148.25 (C), 149.93 (C)], thiadiazole C: [66.34 (CH), 148.91 (C)], 133.99 (C=C), 168.98 (C=O), 170.75 (C=O); MS(ESI-*m/z*): (M+1)⁺: 1370.53; Analysis (% Calculated/found) for C₆₂H₇₂N₁₂O₁₆S₄ (Mw 1369.57) C: 54.37/54.43, H: 5.30/5.26, N: 12.27/12.33

***N,N'*-(5,5'-(2,2'-(2-(1,3-Bis(1-(3-acetyl-5-(*N*-methylacetamido)-2,3-dihydro-1,3,4-thiadiazol-2-yl)naphthalene-2-yloxy)propan-2-ylidene)propane-1,3-diyl)bis(oxy)bis(naphthalene-2,1-diyl))bis(4-acetyl-4,5-dihydro-1,3,4-thiadiazole-5,2-diyl))bis(*N*-methylacetamide)**

(5g). The solid obtained was washed with H₂O and recrystallized from ethyl alcohol, yield: 0.30 g (52 %); m.p. 221 °C; IR (KBr) (ν, cm⁻¹), 3054 (Ar-CH), 1671-1656 (C=O); ¹H-NMR (DMSO-d₆) δ (ppm) 2.07 (s, 12H, CH₃), 2.16 (s, 12H, CH₃), 3.49 (s, 12H, N-CH₃), 5.22 (s, 8H, OCH₂), 7.25 (m, 4H, thiadiazole), 7.25-7.76 (m, 24H, ar-H); ¹³C-NMR (DMSO-d₆) δ (ppm) 22.53 (CH₃), 23.27 (CH₃), 35.92 (N-CH₃), 67.83 (O-CH₂), ar-C: [115.84 (C), 118.05 (CH), 120.33 (CH), 122.88 (CH), 123.89 (CH), 127.13 (CH), 127.15 (C), 129.61 (CH), 131.53 (C), 154.53 (C)], 137.62 (C=C), 169.23 (C=O), 170.96 (C=O); MS(ESI-*m/z*): (M+Na)⁺: 1472.66 Analysis (% Calculated/found) for C₇₄H₇₂N₁₂O₁₂S₄ (Mw 1449.70) C: 61.31/61.28, H: 5.01/5.06, N: 11.59/11.65

Microbial test studies

Antimicrobial activity assessment

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 (CHCl₃) to prepare chemicals stock solution of 4.0-14.0 mg/ml.

Simple susceptibility screening test using agar-well diffusion method⁶³ as adapted earlier⁶⁴ was used. Each microorganism was suspended in Mueller Hinton (MH) (Difco, Detroit, MI) broth and diluted approximately 10⁶ colony forming unit (cfu) per ml. They were "flood-inoculated" onto the surface of MH agar and Sabouraud Dextrose Agar (SDA) (Difco, Detroit, 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 μ l 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 μ g) and Triflucan (5 μ g) were standard drugs. DMF and CHCl₃ were used as solved control.

Results of antimicrobial activity

As seen in Table 1, some chemicals showed slight antimicrobial activity against Gram-positive and Gram-negative bacteria, but no antifungal activity except **3d** and **4e** was observed against yeast-like fungi. The bacterial species were chosen to represent the most common pathogenic and undesirable organisms associated with food. *C. albicans* was included because of its predominance as a common human pathogen. Chemicals **3a**, **3b**, **3c**, **3d** and **4h** were slight active on *E. coli*, *K. pneumonia* and *P. aeruginos*, also Gram negative bacteria. On the other hand **4b** was found slight effective against *S. aureus*, and **5a**, **5b** and **5g** against *E. faecalis*, also Gram positive bacteria. *B. cereus* a Gram positive spore forming bacterium was the most resistant bacterial strain against all tested substances. Neither of the chemicals was able to show activity against of *B. cereus*.

Table 1. Antimicrobial activities for all compounds

No	Sol.	Stok Sol. (mg/1ml)	Test sol. (mg /50 μ l)	Microorga nisms and inhibition zone (mm)						
				Eco	Kp	Pa	Ef	Sa	Bs	Ca
3a	DMF	10,7	535	+	+	+	-	-	-	-
3b	"	11,9	595	+	+	+	-	-	-	-
3c	"	11,1	555	+	+	+	-	-	-	-
3d	"	14,0	700	+	+	+	-	-	-	+
3e	"	9,0	450	-	-	-	-	-	-	-
3f	"	9,2	450	-	-	-	-	-	-	-
3g	"	10,0	500	-	-	-	-	-	-	-
3h	"	10,2	510	-	-	-	-	-	-	-
4a	"	10,5	525	-	-	-	-	-	-	-
4b	"	8,7	435	-	+	+	-	+	-	-
4e	"	13,0	650	-	+	-	-	-	-	+
4f	"	10,7	535	-	+	-	-	-	-	-
4g	"	10,4	520	-	-	-	-	-	-	-
4h	CHCl ₃	9,4	475	+	+	+	+	-	-	-
5a	"	4,9	245	-	-	-	+	-	-	-
5b	"	12	600	-	-	-	+	-	-	-
5e	"	11,0	550	-	-	-	-	-	-	-
5f	"	6,7*	670	-	-	-	-	-	-	-
5g	"	9,0	450	+	+	-	+	-	-	-
Ceftazidime				+++	+++	+++	+++	+++	+++	
Triflucan										+++

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. Results were interpreted in terms of the diameter of the inhibition zone: (-): < 5.5 mm; (+): 5.5-10 mm; (++) : 11-15 mm; (+++): \geq 15 mm.

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