Synthesis, Structural Characterization, and Biological Evaluation of Novel Substituted 1,3-Thiazole Derivatives Containing Schiff Bases

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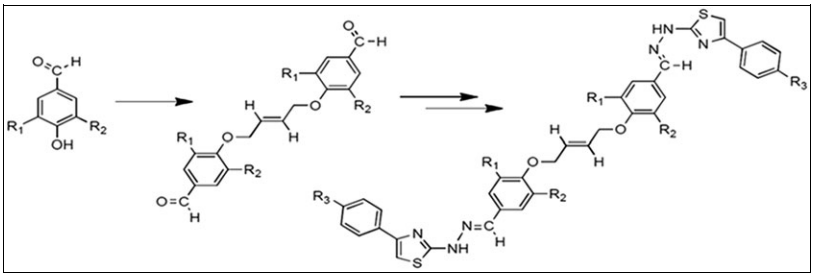

In this study, thiazole derivatives containing Schiff bases **(7–9 a-f)** were synthesized in moderate to high yields (49–94%) using the Hantzsch reaction with thiosemicarbazone derivatives **(5a-c)** and 2-bromo-1-phenylethanone derivatives **(6a-f)**. The structures of synthesized compounds were elucidated by IR, ^{1}H NMR, ^{13}C NMR, elemental analyses, mass spectroscopy and X-ray diffraction analysis techniques. Moreover, the synthesized compounds were tested for their *in vitro* antifungal activity and most of them exhibited moderate to good activity against *Fusariumoxysporumf.sp. lycopersici.*

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INTRODUCTION

In recent years, despite significant increases in the discovery of compounds with biological activities, their uses were quite limited owing to the development of resistance against these compounds and the presence of various side effects. For these reasons, great efforts have been made by chemists to synthesize compounds exhibiting biological activities that have the potential to be used in pharmaceutical chemistry.

Thiazole is a five-member aromatic heterocyclic compound with the molecular formula of C_3H_3NS. Because it has both an electron-withdrawing group (C=N) and an electron-donating group (–S–), it is quite reactive in chemical reactions [1]. Thiazole and its derivatives, which are among the most widely known heterocyclic systems with various biological activities, have particularly become the center of attention in recent years as structures of pharmacological and technological importance [2–5].

The syntheses of thiazole and its heterocyclic derivatives have been increasingly investigated for years owing to their various biological activities, including antifungal [6,7], antibacterial [8,9], anti-inflammatory [10], anticonvulsant [11], anti-cancer [12–17], antihypertensive [18], anti-HIV [19], and anti-tuberculosis properties [20,21]. Additionally, according to various studies conducted on thiazole and its derivatives, some of the compounds reportedly can be used to make polymers, liquid crystals, fluorescent dyes, herbicides, and insecticides [22–25].

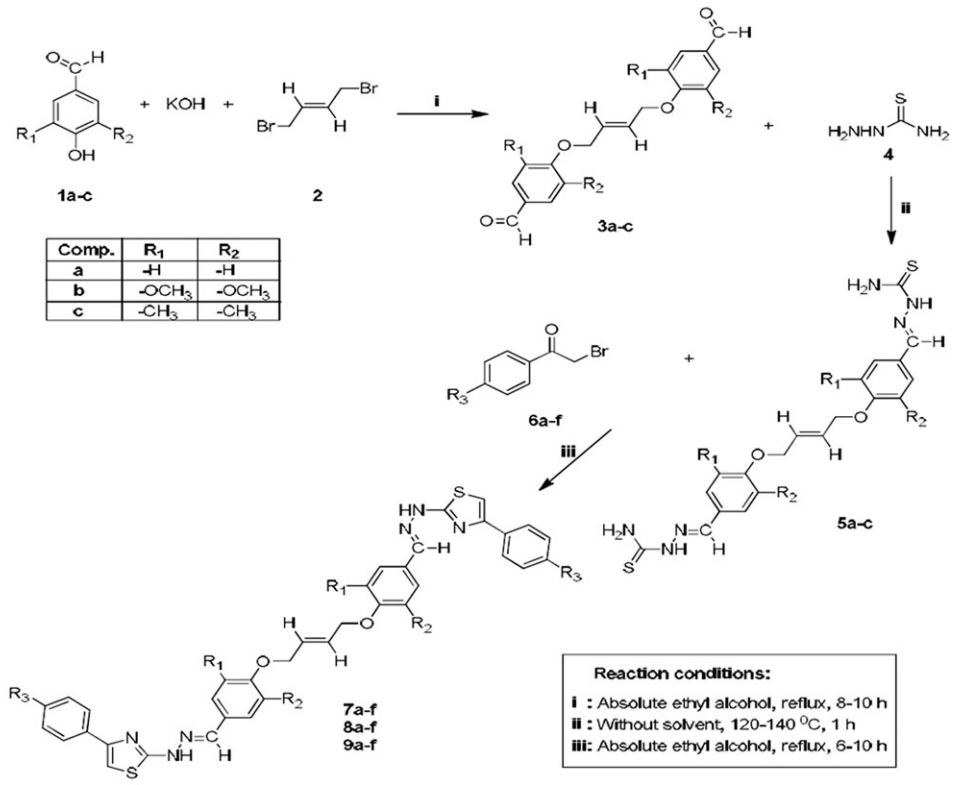
Schiff bases are known as products obtained from the condensation of primary amines with active carbonyl groups. Schiff bases are an azomethine group with a general formula of RHC=N–R′ that contains various substituted groups, such as R and R′ (alkyl, aryl, cycloalky, or heterocyclic groups) [26,27]. They are considered by the scientific community to be extremely important owing to their physiological and pharmacological characteristics. Schiff bases are used in various industrial processes including the manufacturing of certain optic materials, conductive polymers, and dyes [28–31]. In addition, they also possess numerous pharmacological characteristics, such as antifungal, antibacterial, anti-cancer, and antiviral activities [32–35].

In the light of the important data gathered through the research of the literature, the main objective of this study was to synthesize and characterize together various substituted groups containing thiazole and Schiff bases that possess potential biological activities (Scheme 1). We believe that these synthesized compounds may contribute greatly to the areas of medicine and industry owing to their properties introduced to the heterocycle.

RESULTS AND DISCUSSION

In the first portion of the study, (*E*)-dibenzaldehyde derivatives (**3a–c**) were obtained in high yields (70–75%) from the reaction of 4-hydroxybenzaldehyde derivatives (**1a–c**) with (*E*)-1,4-dibromobut-2-ene in the presence of KOH and absolute alcohol (Scheme 1). In the IR spectral data of these compounds, the most significant data expected from (*E*)-dibenzaldehyde compounds (**3a–c**) was the development of an absorption band belonging to aldehydes –CH (Fermi doublet) in the range of 2742–2862 cm^{-1}. Parallel to this occurrence, carbonyl group (C=O) absorption bands that bear an important and specific band quality in (*E*)-dibenzaldehyde derivatives were observed in the range of 1679–1686 cm^{-1} owing to the symmetrical quality of the molecule. While =CH absorption bands belonging to the aromatic ring in these compounds were observed in the range of 3031–3070 cm^{-1}, =C–O–C bands were detected in the range of 1247–1326 and 1215–1223 cm^{-1}. In addition, the structures of compounds **3a–c** were also confirmed with the assistance of ^{1}H NMR spectroscopy. In the ^{1}H NMR spectra of compounds **3a–c**, aldehyde group (CHO) protons were observed as a singlet corresponding to two protons in the range of 9.85–9.86 ppm. The values of this chemical shift bear the quality of specific chemical shifts for aldehyde protons. Vinylic protons (–HC=CH–) found in the ethylene double bond in compound **3a** were established to be completely equal and identified as a singlet at 6.09 ppm corresponding to two protons. The methylene group (–OCH_2) proton signals belonging to this compound were recorded as a singlet corresponding to four protons at 4.73 ppm. Vinylic protons found in ethylene double bonds in compounds **3b** and **3c** were different from **3a**; they did, however, conform to expectations and were established as a triplet corresponding to two protons as a result of methylene interaction. Additionally, methylene group protons were established as a doublet of doublet corresponding to four protons in compounds **3b** and **3c**; this occurrence was expected from the structure as a result of the interaction of vinylic protons in the range of 4.43–4.51 ppm.

Scheme 1. Synthetic procedure of novel compounds **3** (**a–c**), **5** (**a–c**), and (**7–9**) **a–f**.



Comp.	R_1	R_2
a	-H	-H
b	$-OCH_3$	$-OCH_3$
c	$-CH_3$	$-CH_3$

Comp.	R_1	R_2	R_3	Comp.	R_1	R_2	R_3	Comp.	R_1	R_2	R_3
7a	-H	-H	-H	**8a**	$-OCH_3$	$-OCH_3$	-H	**9a**	$-CH_3$	$-CH_3$	-H
7b	-H	-H	-Br	**8b**	$-OCH_3$	$-OCH_3$	-Br	**9b**	$-CH_3$	CH_3	-Br
7c	-H	-H	-Cl	**8c**	$-OCH_3$	$-OCH_3$	-Cl	**9c**	$-CH_3$	CH_3	-Cl
7d	-H	-H	$-OCH_3$	**8d**	$-OCH_3$	$-OCH_3$	$-OCH_3$	**9d**	$-CH_3$	CH_3	$-OCH_3$
7e	-H	-H	-Ph	**8e**	$-OCH_3$	$-OCH_3$	-Ph	**9e**	$-CH_3$	CH_3	-Ph
7f	-H	-H	$-NO_2$	**8f**	$-OCH_3$	$-OCH_3$	$-NO_2$	**9f**	$-CH_3$	CH_3	$-NO_2$

In the ^{13}C NMR spectra of compounds **3a–c**, methylene group carbon peak signals were recorded at 67.99–72.51 ppm as expected from sp^3 hybridized carbons. Also in this region, $–OCH_3$ carbon, which bonded to the aromatic ring in compound **3b**, was revealed at 56.53 ppm, and $–CH_3$ carbon peaks found in the aromatic ring in compound **3c** were observed at 16.62 ppm. On the other hand, sp^2 hybridized vinylic carbons in compounds **3a–c** were found in the range of 128.75–129.47 ppm. In these compounds, C=O carbon signals bearing the aldehyde functional group were recorded at 191.74–192.50 ppm as expected. In addition, the structure of compound **3b** ($C_{22}H_{24}O_8$) was confirmed by X-ray diffraction analysis. The compound **3b** crystallized in the monoclinic space group $P2_1/c$ with $a = 8.5127(5)$ Å, $b = 15.4359(8)$ Å, $c = 15.6658(7)$ Å, $\alpha = 90°$, $\beta = 92.208(3)°$, and $\gamma = 90°$. The structure of compound **3b** [36] (Fig. 1) crystallized in the monoclinic space group $P2_1/c$ with four molecules in the unit cell. Crystallographic data of compound **3b** are shown in Table 1.

In the second part of the study, thiosemicarbazone derivatives (**5a–c**) having the role of target compounds were synthesized in high yields (74–84%) by a condensation reaction of (*E*)-dibenzaldehyde derivatives (**3a–c**) with thiosemicarbazide (**4**) (Scheme 1).

In the IR spectral data of compounds **5a–c**, it was established that C=O absorption bands of the aldehyde functional group used in the synthesis of these compounds completely disappeared, and instead, bands belonging to the azomethine group (C=N) occurred in the range of 1576–1618 cm^{-1}. Another significant sample of data related to the formation of the thiosemicarbazone derivatives (**5a–c**) was the development of symmetrical and asymmetrical absorption bands, which were observed in the range of 3150–3264 cm^{-1} and belong to the $–NH_2$ group. In these compounds, –NH absorption bands were observed between 3157 and 3170 cm^{-1}. Although the IR spectral values given for compounds **5a–c** were in line with the data found in the literature on this type of compound, the band in the range of 760–790 cm^{-1} given for the thione group (C=S) in the literature does not possess a specific band quality [37]. In another literature resource, the C=S absorption band was stated to be in the range of 1272–1276 cm^{-1} [38]. As it did not bear a specific band characteristic, the spectral data concerning C=S absorption bands were not presented in the Experimental section.

In the ^1H NMR spectra belonging to these compounds, it was observed that aldehyde protons (CHO) in compounds **3a–c** occurring at approximately 9.85–9.86 ppm (used in synthesis of the thiosemicarbazone derivatives) were replaced by proton peaks in the azomethine group (CH=N) occurring in the range of 7.92–7.97 ppm. On the other hand, –NH protons in compounds **5a–c** gained a relatively acidic proton characteristic and appeared as a singlet between 11.28 and 11.40 ppm. In addition, protons (NH_2) that bonded to nitrogen in thiosemicarbazone derivatives (**5a–c**) appeared as equivalent protons, and they were observed in the spectral data as a singlet in the ranges of 7.89–8.12 and 8.08–8.59 ppm. In the D_2O-exchangeable spectra of compounds **5a–c**, the singlet belonging to –NH protons disappeared in the range of 11.28–11.40 ppm, and $^4NH_2$ protons appeared at 7.89–8.12 and 8.08–8.59 ppm, supporting our suggested structures.

In the ^{13}C NMR spectra of compounds **5a–c**, vinylic carbons, $–OCH_2$ carbons, and carbons belonging to aromatic compounds were observed to manifest great similarities with spectral data previously detected in compounds **3a–c**. However, the most significant samples of the spectral data that differed in compounds **5a–c** were the peaks that occurred in the range of 178.09–178.21 ppm belonging to the thione group (C=S). These samples of spectral data represented quite specific values in thiosemicarbazone derivatives, thiourea, and thioamides [39–43]. On the other hand, carbon signals belonging to the azomethine group (C=N) were recorded at 142.47–142.63 ppm. Additional spectral data belonging to the carbon skeleton completely verified the molecular structures we suggested.

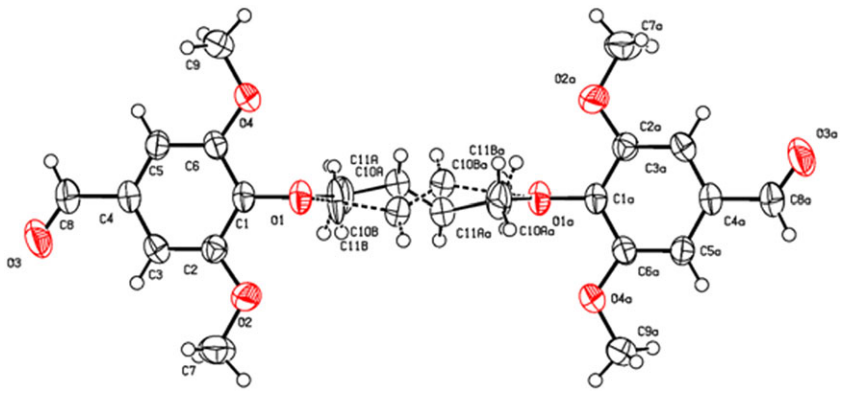


Figure 1. ORTEP-III diagram of compound **3b**. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Table 1

Crystallographic data for compound **3b**.

Formula	$C_{22}H_{24}O_8$
Formula weight	416.42 (a.k.b)
Temperature	296 K
Wavelength (Å)	MoK_α, 0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell dimensions	
a (Å)	8.5127(5)
b (Å)	15.4359(8)
c (Å)	15.6658(7)
α (°)	90
β (°)	92.208(3)
γ (°)	90
Volume	1028.49(2) $Å^3$
Z (molecule/cell)	4
Calculated density	1.340 g cm^{-3}
F(000)	440
Crystal size	0.17 × 0.21 × 0.28 (mm)
Index ranges	$-11 \le h \le 10$, $-20 \le k \le 18$, $10 \le l \le 10$
Reflections collected	20,178
Independent reflections	2572
Reflections observed [$I \ge 2\sigma(I)$]	2019
R_{int}	0.057
R [$I > 2\sigma(I)$]	0.072
Rw [$I > 2\sigma$(I)]	0.143
Goodness-of-fit on indicator	1.045
Structure determination	SHELXL97 [47]
Extinction factor	0.001(2)
$(\Delta\sigma)_{max}$, $(\Delta\sigma_{min})$ (e/$Å^3$)	0.399, −0.363
CCDC	1,057,169

In the final portion of the study, 1,3-thiazole derivatives containing Schiff bases (**7–9a–f**), were synthesized using the Hantzsch reaction by the reaction of thiosemicarbazone derivatives (**5a–c**) with 2-bromo-1-phenylethanone derivatives (**6a–f**) in moderate to high yields without using catalysts (Scheme 1). The Hantzsch reaction is the most common method for the synthesis of thiazole derivatives, which involves the cyclization and condensation reaction of thioamides with haloketones [44,45]. The reaction mechanism is presented in Scheme 2.

In the IR spectral data of compounds **7–9a–f**, the most important evidence that the thiazole ring occurred was the disappearance of the symmetrical and asymmetrical $^4NH_2$ and –NH absorption bands observed in the range of 3150–3264 cm^{-1}. Instead, –NH absorption bands belonging to the 1,3-thiazole ring were observed between 3105 and 3188 cm^{-1}. The structures of these compounds were also confirmed by ^{1}H NMR spectroscopy. In the ^{1}H NMR spectra of compounds **7–9a–f**, chemical shift values belonging to the relatively acidic –NH protons that reside next to the thiazole ring were observed in the range of 12.09–12.29 ppm. These data provide the most important evidence for the cyclization, and they are confirmed in the literature [46]. Also, in the D_2O-exchangeable spectra of compounds **7–9a–f**, it was observed that the –NH band completely disappeared from the spectrum in the range of 12.09–12.29 ppm. Another important data point reflecting the process of cyclization was the C^5H proton peak in the thiazole ring. The C^5H proton signals were recorded at 7.11–7.84 ppm as a singlet corresponding to two protons. Integral ratios and chemical shifts of aromatic and aliphatic protons of all compounds in ^{1}H NMR spectra were observed as expected. Other ^{1}H NMR results belonging to compounds **7–9a–f** are given in detail in the Experimental section.

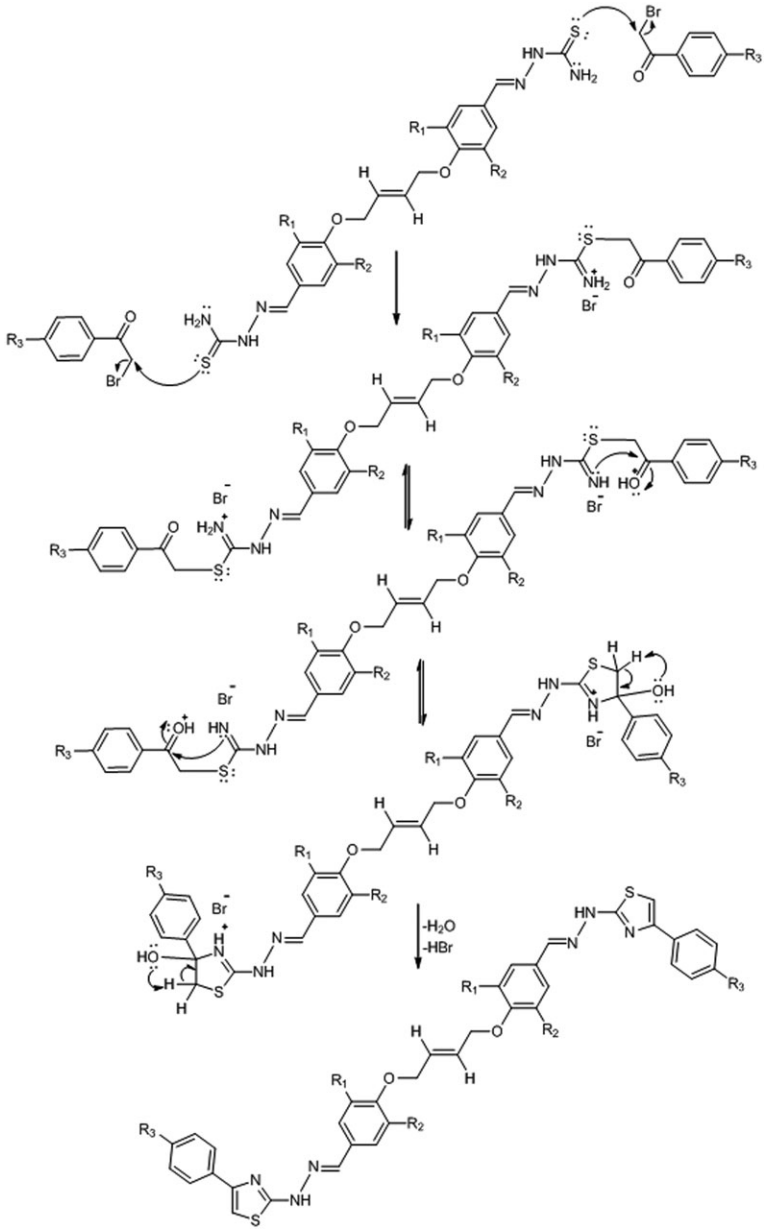
In the ^{13}C NMR spectral data of compounds **7–9a–f**, the peaks disappeared, which were observed in the range of 178.09–178.21 ppm belonging to thione group (C=S) carbon found in thiosemicarbazone derivatives used in the synthesis of the thiazole ring. Additionally, signals of C^5 carbon, C^4 quaternary carbon, and C^2 quaternary carbon belonging to the thiazole ring were recorded in the ranges of 101.76–109.01, 141.17–142.11, and 168.17–169.20 ppm, respectively. These data are consistent with the data given in the literature for the thiazole ring [47]. Other ^{13}C NMR spectral data of compounds **7–9a–f are** provided in detail in the Experimental section. The spectra of all compounds are given in the Supporting Information.

Moreover, the synthesized compounds were tested for their *in vitro* antifungal activity against *Fusarium oxysporum* f.sp. *lycopersici* (FOL). Antifungal activity values (inhibition zone, percentage inhibition, and activity index) of 24 compounds are presented in Table 2. All compounds demonstrated different levels of antifungal activities against FOL. Each compound received three different doses (10,000, 5000, and 2500 ppm), and an increase in the doses for the compounds of antifungal activities showed an increase in values. Thiram 80% (reference drug) was used against FOL as a positive control and inhibited 84.90%. Dimethyl sulfoxide (DMSO) was used as a negative control, and antifungal activity was not observed. According to the results obtained in the experiment, all compounds showed antifungal effects when compared with positive control. The following values were observed regarding the inhibition of FOL: compounds **3a–c** between 20.38 and 47.59%; **5a–c** between 28.11 and 55.75%; **7a–f** between 30.19 and 59.87%; **8a–f** between 27.64 and 61.88%; and **9a–f** between 21.04 and 58.74%. Compounds **7–9** (**a–f**) were observed to be more effective than compounds **3a–c** and **5a–c**. Although the antifungal activity of these compounds was lower than that of the reference drug, the inhibitory activity of title compounds could be further improved by incorporating appropriate functional groups.

EXPERIMENTAL

The reactions were carried out under a nitrogen atmosphere using standard Schlenk techniques. The ^{1}H NMR and ^{13}C NMR spectra of the compounds were recorded in DMSO-d_6 using an Agilent NMR VNMRS spectrometer

Scheme 2. Hantzsch synthetic approach of thiazole derivatives.



(Santa Clara, CA) at 400 and 100 MHz, respectively. Chemical shift values are given in ppm (δ) with tetramethylsilane as internal standard. The IR spectra were measured in attenuated total reflection (ATR) using a Perkin Elmer FT-IR Spectrometer Frontier (Waltham, MA). The mass spectra were measured with a Thermo TSQ Quantum Access Max LC-MS/MS spectrometer (Encino, CA) equipped with ethyl alcohol and chloroform as solvents. Elemental analyses were performed on a LECO 932 CHNS (Leco-932, St. Joseph, MI) instrument, and the results were within ±0.4% of the theoretical values. Melting points were recorded on a Thermo Scientific IA9000 series apparatus and were uncorrected. All of the chemicals were obtained from Merck Chemicals (Darmstadt, Germany).

Crystallographic analysis. All diffraction measurements were performed on the goniometer of a Bruker AXS APEX CCD (Madison, WI) using graphite monochromated MoK_α radiation ($\lambda = 0.71073$ Å) at room temperature (296 K). The data reduction was performed with the Bruker SMART software package (Madison, WI) [48]. The structure was solved using direct methods with SHELXS-97 (Göttingen, Germany) [49], and all non-hydrogen atoms were refined anisotropically by the full-matrix least squares procedure based on F^2 using SHELXL97 (Göttingen, Germany). Molecular design was acquired using ORTEP-III [50].

Fungal isolate. *Fusarium oxysporum* f.sp. *lycopersici* was used for this experiment. The fungal pathogen was isolated from tomatoes in Antalya, Turkey. The pathogen

Table 2

Antifungal activity values (IZ, PI, and AI) against *Fusarium oxysporum* f.sp. *lycopersici* of compounds **3a–c**, **5a–c**, **7a–f**, **8a–f**, and **9a–f**.

Compounds (mg/mL)	10 mg/mL (10,000 ppm)			5 mg/mL (5000 ppm)			2.5 mg/mL (2500 ppm)		
	IZ (mm)	PI (%)	AI	IZ (mm)	PI (%)	AI	IZ (mm)	PI (%)	AI
3a	11.22	44.05	0.44	8.90	34.94	0.35	6.96	27.33	0.27
3b	12.12	47.59	0.48	10.35	40.64	0.41	8.19	32.16	0.32
3c	10.41	40.87	0.41	8.12	31.88	0.32	5.19	20.38	0.20
5a	11.66	45.78	0.46	9.75	38.28	0.38	8.25	32.39	0.32
5b	11.67	45.82	0.46	9.87	38.75	0.39	7.16	28.11	0.28
5c	14.20	55.75	0.56	12.73	53.91	0.54	12.03	47.23	0.47
7a	15.25	59.87	0.60	12.75	50.06	0.50	11.00	43.19	0.43
7b	15.00	58.89	0.59	11.74	46.09	0.46	7.69	30.19	0.30
7c	11.94	46.88	0.47	9.03	35.45	0.35	8.65	33.96	0.34
7d	12.95	50.84	0.51	10.17	39.93	0.40	8.12	31.88	0.32
7e	13.78	54.10	0.54	12.28	48.21	0.48	8.96	35.18	0.35
7f	14.27	56.03	0.56	10.79	42.36	0.42	9.02	35.41	0.35
8a	14.69	57.68	0.58	12.00	47.11	0.47	8.00	31.41	0.31
8b	15.76	61.88	0.62	14.05	59.09	0.59	12.34	48.45	0.48
8c	13.10	51.43	0.51	10.68	41.93	0.42	9.25	36.32	0.36
8d	13.16	51.67	0.52	10.89	42.76	0.43	7.04	27.64	0.28
8e	13.63	53.51	0.54	11.31	44.41	0.44	8.87	34.83	0.35
8f	12.34	48.45	0.48	11.24	44.13	0.44	9.32	36.59	0.37
9a	13.27	52.10	0.52	11.87	46.60	0.47	11.69	45.90	0.46
9b	11.13	43.70	0.44	7.50	29.45	0.29	5.36	21.04	0.21
9c	14.96	58.74	0.59	11.32	44.44	0.44	9.89	38.83	0.39
9d	13.17	51.71	0.52	11.22	44.05	0.44	7.92	31.10	0.31
9e	14.88	58.42	0.58	12.04	47.27	0.47	7.96	31.25	0.31
9f	14.78	58.03	0.58	12.92	50.73	0.51	10.05	39.46	0.39
C+ (Thiram)	**25.47**	**84.90***	**0.85**	**25.47**	**84.90***	**0.85**	**25.47**	**84.90***	**0.85**
C− (DMSO)	0	0	0	0	0	0	0	0	0

Developments of mycelium were calculated PI and AI for C+.
IZ, inhibition zone; PI, percentage of inhibition; AI, activity index; C+, positive control; C−, negative control.
*Each holes were opened 30 mm far from center on the potato dextrose agar plate. Thiram was used as a reference drug and shown in bold font.

was grown on a potato dextrose agar medium at 22 ± 2°C for about 7 days. The antifungal activities of the compounds were determined by the agar well diffusion method [51]. Antifungal activity calculations (percentage of inhibition, activity index) are provided in detail in the Supporting Information.

General procedure for the synthesis of (E)-4,4′-(but-2-ene-1,4-diylbis(oxy))substituted benzaldehyde derivatives (3a–c). In a two-necked flask, 4-hydroxybenzaldehyde derivatives **1a–c** (0.1 mol) and KOH (0.1 mol) were dissolved in absolute ethanol (100 mL), and the solution was stirred for 30 min at room temperature. (*E*)-1,4-Dibromobut-2-ene **2** (0.05 mol) was dissolved in absolute ethanol (25 mL) and added drop by drop to this solution at room temperature with the assistance of a dropping funnel. The mixture was then refluxed and stirred for 8–10 h. The progress of the reaction was monitored by thin-layer chromatography (TLC) at appropriate time intervals. After completion of the reaction, the solution was filtered, and the solid matter was obtained. It was washed with deionized water, ethanol, and diethyl ether, respectively. The solid matter was recrystallized from the appropriate solvent. The synthesized compounds were dried with P_2O_5 in a vacuum oven. The physical properties and spectral data of the obtained products are listed subsequently.

(E)-4,4′-(But-2-ene-1,4-diylbis(oxy))dibenzaldehyde (3a). This compound was obtained as a white solid, yield 10.67 g (72%), mp 139–140°C [from dimethylformamide (DMF)-EtOH, 4:1]; IR (ATR, cm^{-1}): 3070 (Ar-CH), 2925 (Aliph. CH), 2827–2745 (CHO), 1679 (C=O), 1601 (CH=CH), 1247, 1218 (=C–O–C); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 4.73 (s, 4H, O–CH_2), 6.09 (s, 2H, CH=CH), Ar-H [7.12 (d, J = 5.2 Hz, 4H), 7.84 (dd, J = 3.6, 2.0 Hz, 4H)], 9.85 (d, J = 3.6 Hz, 2H, CHO); ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 67.99 (O–CH_2), Ar-C [115.61 (CH), 130.20 (C), 132.23 (CH), 163.51 (C)], 128.75 (CH=CH), 191.74 (C=O). MS: m/z 319.28 (M^+ + Na, 100). *Anal*. Calcd. for $C_{18}H_{16}O_4$: C, 72.96; H, 5.44. Found: C, 72.94; H, 5.49.

(E)-4,4′-(But-2-ene-1,4-diylbis(oxy))bis(3,5-dimethoxybenzaldehyde) (3b). This compound was obtained as light yellow crystals, yield 15.61 g (75%), mp 162–163°C (from DMF-EtOH, 3:2); IR (ATR, cm^{-1}): 3031 (Ar-CH), 2937 (Aliph. CH), 2849–2750 (CHO), 1686 (C=O), 1586 (CH=CH), 1117 (–OCH_3), 1326, 1223 (=C–O–C); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 3.82 (s, 12H, O–CH_3), 4.51 (dd, J = 1.6, 1.2 Hz, 4H, O–CH_2), 5.92 (t,

J = 1.2 Hz, 2H, CH=CH), Ar-H [7.21 (s, 4H)], 9.86 (s, 2H, CHO); ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 56.53 (O–CH_3), 72.51 (O–CH_2), Ar-C [107.15 (CH), 132.13 (C), 141.86 (C), 153.87 (C)], 129.47 (CH=CH), 192.31 (C=O). MS: *m/z* 439.32 (M^+ + Na, 100). *Anal*. Calcd. for $C_{22}H_{24}O_8$: C, 63.45; H, 5.81. Found: C, 63.49; H, 5.87.

(E)-4,4′-(But-2-ene-1,4-diylbis(oxy))bis(3,5-dimethylbenzaldehyde) (3c). This compound was obtained as a white solid, yield 12.34 g (70%), mp 121–122°C (from DMF-EtOH, 1:6); IR (ATR, cm^{-1}): 3035 (Ar-CH), 2970 (Aliph. CH), 2862–2742 (CHO), 1686 (C=O), 1594 (CH=CH), 1299, 1215 (=C–O–C); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 2.28 (s, 12H, CH_3), 4.44 (dd, J = 1.6, 1.2 Hz, 4H, O–CH_2), 6.13 (t, J = 1.2 Hz, 2H, CH=CH), Ar-H [7.59 (s, 4H)], 9.85 (s, 2H, CHO); ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 16.62 (CH_3), 72.14 (O–CH_2), Ar-C [130.75 (C), 132.25 (C), 132.49 (CH), 161.17 (C)], 129.26 (CH=CH), 192.50 (C=O). MS: *m/z* 375.37 (M^+ + Na, 100), 353.32 (M^+ + 1, 25). *Anal*. Calcd. for $C_{22}H_{24}O_4$: C, 74.98; H, 6.86. Found: C, 74.95; H, 6.89.

General procedure for the synthesis of (2*E*,2′*E*)-2,2′-((((*E*)-but-2-ene-1,4-diylbis(oxy))bis(substituted-4,1-phenylene))bis (methanylylidene)) bis(hydrazinecarbothioamide) derivatives (5a–c). Compounds **5a–c** were synthesized according to a method given in the literature [52]. In a round-bottomed flask, compounds **3a–c** (0.017 mol) and thiosemicarbazide **4** (0.051 mol) were heated to 120–140°C without solvent in an oil bath and stirred for 1 h. After the completion of the reaction, DMF (20 mL) was added to the reaction content and dissolved. Water was then added to the solution, and a solid precipitated. The solution was filtered, and the solid was obtained. The solid was washed with warm water and absolute ethanol to remove excess thiosemicarbazide and impurities. The solid was recrystallized from the appropriate solvent. The synthesized compounds were dried with P_2O_5 in a vacuum oven. The physical properties and spectral data of the obtained products are listed subsequently.

(2E,2′E)-2,2′-((((E)-But-2-ene-1,4-diylbis(oxy))bis(4,1-phenylene)) bis(methanylylidene))bis(hydrazinecarbothioamide) (5a). This compound was obtained as a white solid, yield 6.32 g (84%), mp 260–261°C (from DMF); IR (ATR, cm^{-1}): 3264–3150 (NH_2), 3157 (–NH–), 3026 (Ar-CH), 2970 (Aliph. CH), 1601 (C=N), 1534 (CH=CH), 1234, 1170 (=C–O–C); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 4.64 (s, 4H, O–CH_2), 6.06 (s, 2H, CH=CH), Ar-H [6.96 (d, J = 6.4 Hz, 4H), 7.71 (d, J = 7.2 Hz, 4H)], 7.97 (s, 2H, CH=N), 7.89 (s, 2H, NH_2), 8.08 (s, 2H, NH_2), 11.28 (s, 2H, –NH); ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 67.73 (O–CH_2), Ar-C [115.27 (CH), 128.77 (C), 136.19 (C), 160.01 (C)], 129.36 (CH=CH), 142.59 (CH=N), 178.09 (C=S). MS: *m/z* 443.23 (M^+ + 1, 100). *Anal*. Calcd. for $C_{20}H_{22}N_6O_2S_2$: C, 54.28; H, 5.01; N, 18.99. Found: C, 54.34; H, 5.08; N, 19.03.

(2E,2′E)-2,2′-((((E)-But-2-ene-1,4-diylbis(oxy))bis(3,5-dimethoxy-4,1-phenylene))bis(methanylylidene))bis(hydrazinecarbothioamide) (5b). This compound was obtained as a white solid, yield 7.17 g (75%), mp 210–211°C (from DMF-EtOH, 3:1); IR (ATR, cm^{-1}): 3309–3159 (NH_2), 3170 (–NH–), 3027 (Ar-CH), 2937 (Aliph. CH), 1576 (CH=CH), 1528 (C=N), 1230, 1160 (=C–O–C); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 3.79 (s, 12H, O–CH_3), 4.39 (s, 4H, O–CH_2), 5.90 (s, 2H, CH=CH), Ar-H [7.07 (s, 4H)], 7.93 (s, 2H, CH=N), 8.06 (s, 2H, NH_2), 8.20 (s, 2H, NH_2), 11.40 (s, 2H, –NH); ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 56.57 (O–CH_3), 72.53 (O–CH_2), Ar-C [105.09 (CH), 129.39 (C), 138.17 (C), 153.71 (C)], 130.14 (CH=CH), 142.63 (CH=N), 178.21 (C=S). MS: *m/z* 562.04 (M^+, 100). *Anal.* Calcd. for $C_{24}H_{30}N_6O_6S_2$: C, 51.23; H, 5.37; N, 14.94. Found: C, 51.18; H, 5.40; N, 14.99.

(2E,2′E)-2,2′-((((E)-But-2-ene-1,4-diylbis(oxy))bis(3,5-dimethyl-4,1-phenylene))bis(methanylylidene))bis(hydrazinecarbothioamide) (5c). This compound was obtained as a white solid, yield 6.26 g (74%), mp 218–219°C (from DMF-EtOH, 3:1); IR (ATR, cm^{-1}): 3259–3156 (NH_2), 3168 (–NH–), 3032 (Ar-CH), 2970 (Aliph. CH), 1618 (C=N), 1533 (CH=CH), 1299, 1152 (=C–O–C); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 2.22 (s, 12H, CH_3), 4.36 (s, 4H, O–CH_2), 6.10 (s, 2H, CH=CH), Ar-H [7.47 (s, 4H)], 7.92 (s, 2H, CH=N), 8.12 (s, 2H, NH_2), 8.59 (s, 2H, NH_2), 11.32 (s, 2H, –NH); ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 16.54 (CH_3), 72.08 (O–CH_2), Ar-C [128.23 (C), 129.20 (C), 131.44 (CH), 157.43 (C)], 130.03 (CH=CH), 142.47 (CH=N), 178.20 (C=S). MS: *m/z* 521.30 (M^+ + Na, 100). *Anal*. Calcd. for $C_{24}H_{30}N_6O_2S_2$: C, 57.81; H, 6.06; N, 16.85. Found: C, 57.77; H, 6.10; N, 16.89.

General procedure for the synthesis of (*E*)-1,4-bis(4-((*E*)-(2-(4-(4-substitutedphenyl)thiazol-2-yl)hydrazono)methyl)-2,6-disubstitutedphenoxy)but-2-ene derivatives (7a–f, 8a–f, 9a–f). In a two-necked flask, thiosemicarbazone derivatives **5a–c** (0.001 mol) were dissolved in absolute ethanol (50 mL). 2-Bromo-1-phenylethanone derivatives **6a–f** (0.02 mol) were dissolved in absolute ethanol (20 mL) and then added drop by drop to this solution at room temperature with the assistance of a dropping funnel. Then, the mixture was refluxed and stirred for 6–10 h. The progress of reaction was monitored by TLC at appropriate time intervals. The reaction mixture then cooled to the room temperature. It was filtered off and washed with aqueous ammonium hydroxide, deionized water, cold absolute ethanol, and diethyl ether, respectively. The solid was recrystallized from the appropriate solvent. The synthesized compounds were dried with P_2O_5 in a vacuum oven. The physical properties and spectral data derived from the obtained products are listed subsequently.

(E)-1,4-Bis(4-((E)-(2-(4-phenylthiazol-2-yl)hydrazono)methyl) phenoxy)but-2-ene (7a). This compound was obtained as a brown solid, yield 0.56 g (87%), mp 235–237°C (from DMF-EtOH, 3:1); IR (ATR, cm^{-1}): 3147 (–NH–), 3060 (Ar-CH), 2945 (Aliph. CH), 1603 (C=N), 1563 (CH=CH), 1229, 1168 (=C–O–C); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 4.84 (s, 4H, O–CH_2), 6.27 (s, 2H,

CH=CH), 7.57 (s, 2H, thiazole H), Ar-H [7.19 (s, 4H), 8.02 (s, 4H)], thiazole-Ph [7.47 (s, 6H), 7.76 (s, 4H)], 8.16 (s, 2H, CH=N), 12.18 (s, 2H, –NH); ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 67.84 (O–CH_2), thiazole-C [104.72 (CH), 141.57 (C), 169.06 (C)], Ar-C [115.52 (CH), 125.95 (C), 132.43 (CH), 159.44 (C)], thiazole-Ph [127.63 (CH), 128.23 (CH), 129.04 (CH), 139.43 (C)], 128.84 (CH=CH), 146.17 (CH=N). MS: *m/z* 643.64 (M^+ + 1, 100). *Anal*. Calcd. for $C_{36}H_{30}N_6O_2S_2$: C, 67.27; H, 4.70; N, 13.07. Found: C, 67.32; H, 4.77; N, 13.13.

(E)-4-Bis(4-((E)-(2-(4-(4-bromophenyl)thiazol-2-yl)hydrazono) methyl)phenoxy)but-2-ene (7b). This compound was obtained as a light brown solid, yield 0.70 g (87%), mp 248°C (decomp.) (from DMF-EtOH, 3:1); IR (ATR, cm^{-1}): 3105 (–NH–), 3039 (Ar-CH), 2967 (Aliph. CH), 1604 (C=N), 1562 (CH=CH), 1240, 1168 (=C–O–C); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 4.79 (s, 4H, O–CH_2), 6.21 (s, 2H, CH=CH), 7.49 (s, 2H, thiazole H), Ar-H [7.14 (d, J = 8.0 Hz, 4H), 7.92 (d, J = 8.0 Hz, 4H)], thiazole-Ph [7.71 (d, J = 8.0 Hz, 8H)], 8.11 (s, 2H, CH=N), 12.14 (s, 2H, –NH); ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 67.74 (O–CH_2), thiazole-C [104.82 (CH), 141.83 (C), 168.92 (C)], Ar-C [115.53 (CH), 126.44 (C), 127.97 (CH), 159.61 (C)], thiazole-Ph [121.43 (CH), 127.58 (CH), 128.26 (C), 131.96 (C)], 128.84 (CH=CH), 146.59 (CH=N). MS: *m/z* 823.42 (M^+ + Na, 100). *Anal*. Calcd. for $C_{36}H_{28}Br_2N_6O_2S_2$: C, 54.01; H, 3.53; N, 10.50. Found: C, 54.04; H, 3.59; N, 10.55.

(E)-1,4-Bis(4-((E)-(2-(4-(4-chlorophenyl)thiazol-2-yl)hydrazono) methyl)phenoxy)but-2-ene (7c). This compound was obtained as a light brown solid, yield 0.55 g (77%), mp 242°C (decomp.) (from DMF-EtOH, 1:1); IR (ATR, cm^{-1}): 3108 (–NH–), 3057 (Ar-CH), 2986 (Aliph. CH), 1603 (C=N), 1564 (CH=CH), 1241, 1168 (=C–O–C); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 4.78 (s, 4H, O–CH_2), 6.22 (s, 2H, CH=CH), 7.48 (s, 2H, thiazole H), Ar-H [7.14 (d, J = 8.0 Hz, 4H), 7.98 (d, J = 7.6 Hz, 4H)], thiazole-Ph [7.58 (d, J = 8.0 Hz, 4H), 7.71 (d, J = 7.6 Hz, 4H)], 8.11 (s, 2H, CH=N), 12.14 (s, 2H, –NH); ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 67.74 (O–CH_2), thiazole-C [104.64 (CH), 141.81 (C), 168.92 (C)], Ar-C [115.52 (CH), 127.57 (C), 129.05 (CH), 159.61 (C)], thiazole-Ph [127.65 (CH), 128.26 (CH), 132.32 (C), 134.06 (C)], 128.84 (CH=CH), 147.84 (CH=N). MS: *m/z* 713.88 (M^+ + 2, 100). *Anal*. Calcd. for $C_{36}H_{28}Cl_2N_6O_2S_2$: C, 60.76; H, 3.97; N, 11.81. Found: C, 60.83; H, 3.99; N, 11.79.

(E)-1,4-Bis(4-((E)-(2-(4-(4-methoxyphenyl)thiazol-2-yl)hydrazono) methyl)phenoxy)but-2-ene (7d). This compound was obtained as a light brown solid, yield 0.56 g (80%), mp 229°C (decomp.) (from DMF-EtOH, 1:1); IR (ATR, cm^{-1}): 3167 (–NH–), 3023 (Ar-CH), 2929 (Aliph. CH), 1602 (C=N), 1557 (CH=CH), 1242, 1168 (=C–O–C); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 3.92 (s, 6H, O–CH_3), 4.79 (s, 4H, O–CH_2), 6.22 (s, 2H, CH=CH), 7.48 (s, 2H, thiazole H), Ar-H [7.09 (d, J = 8.0 Hz, 4H), 7.91 (d, J = 8.0 Hz, 4H)], thiazole-Ph [7.15 (d, J = 7.6 Hz, 4H), 7.72 (d, J = 7.2 Hz, 4H)], 8.11 (s, 2H, CH=N), 12.09 (s, 2H, –NH); ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 55.56 (O–CH_3), 67.75 (O–CH_2), thiazole-C [104.23 (CH), 141.73 (C), 168.67 (C)], Ar-C [114.39 (CH), 127.73 (C), 130.86 (CH), 159.20 (C)], thiazole-Ph [115.52 (CH), 127.27 (C), 128.19 (CH), 159.54 (C)], 128.84 (CH=CH), 146.92 (CH=N). MS: *m/z* 725.73 (M^+ + Na, 100). *Anal*. Calcd. for $C_{38}H_{34}N_6O_4S_2$: C, 64.94; H, 4.88; N, 11.96. Found: C, 64.89; H, 4.93; N, 12.00.

(E)-1,4-Bis(4-((E)-(2-(4-([1,1'-biphenyl]-4-yl)thiazol-2-yl)hydrazono) methyl)phenoxy)but-2-ene (7e). This compound was obtained as a yellowish brown solid, yield 0.62 g (78%), mp 264–266°C (from DMF-EtOH, 1:2); IR (ATR, cm^{-1}): 3152 (–NH–), 3031 (Ar-CH), 2945 (Aliph. CH), 1604 (C=N), 1573 (CH=CH), 1241, 1168 (=C–O–C); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 4.84 (s, 4H, O–CH_2), 6.26 (s, 2H, CH=CH), 7.52 (s, 2H, thiazole H), Ar-H [7.19 (d, J = 7.6 Hz, 4H), 7.77 (d, J = 7.6 Hz, 4H)], thiazole-Ph [7.87 (d, J = 6.8 Hz, 4H), 8.10 (d, J = 6.4 Hz, 4H)], Ph-Ph [7.52 (bs, 4H)], 7.64 (bs, 6H), 8.16 (s, 2H, CH=N), 12.20 (s, 2H, –NH); ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 67.78 (O–CH_2), thiazole-C [104.52 (CH), 141.94 (C), 168.84 (C)], Ar-C [115.55 (CH), 126.52 (C), 133.82 (CH), 159.58 (C)], thiazole-Ph [126.91 (CH), 128.23 (C), 134.02 (C), 140.42 (C)], Ph-Ph [127.26 (CH), 127.66 (CH), 129.42 (CH), 139.44 (C)], 128.86 (CH=CH), 142.42 (CH=N). MS: *m/z* 817.30 (M^+ + Na, 100). *Anal*. Calcd. for $C_{48}H_{38}N_6O_2S_2$: C, 72.52; H, 4.82; N, 10.57. Found: C, 72.58; H, 4.78; N, 10.55.

(E)-1,4-Bis(4-((E)-(2-(4-(4-nitrophenyl)thiazol-2-yl)hydrazono) methyl)phenoxy)but-2-ene (7f). This compound was obtained as a yellowish brown solid, yield 0.59 g (80%), mp 272°C (decomp.) (from DMF-EtOH, 1:2); IR (ATR, cm^{-1}): 3116 (–NH–), 3027 (Ar-CH), 2921 (Aliph. CH), 1598 (C=N), 1569 (CH=CH), 1233, 1168 (=C–O–C); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 4.83 (s, 4H, O–CH_2), 6.25 (s, 2H, CH=CH), 7.84 (s, 2H, thiazole H), Ar-H [7.19 (d, J = 8.0 Hz, 4H), 7.76 (d, J = 8.0 Hz, 4H)], thiazole-Ph [8.26 (d, J = 8.0 Hz, 4H), 8.42 (d, J = 8.0 Hz, 4H)], 8.17 (s, 2H, CH=N), 12.20 (s, 2H, –NH); ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 67.78 (O–CH_2), thiazole-C [108.75 (CH), 141.17 (C), 169.20 (C)], Ar-C [115.54 (CH), 126.75 (C), 128.32 (CH), 159.67 (C)], thiazole-Ph [124.54 (CH), 127.48 (CH), 146.61 (C), 148.41 (C)], 128.87 (CH=CH), 142.21 (CH=N). MS: *m/z* 733.84 (M^+ + 1, 100). *Anal*. Calcd. for $C_{36}H_{28}N_8O_6S_2$: C, 59.01; H, 3.85; N, 15.29. Found: C, 59.03; H, 3.89; N, 15.32.

(E)-1,4-Bis(2,6-dimethoxy-4-((E)-(2-(4-phenylthiazol-2-yl) hydrazono)methyl)phenoxy) but-2-ene (8a). This compound was obtained as an orange solid, yield 0.46 g (60%), mp 172–174°C (from DMF-EtOH, 1:5); IR (ATR, cm^{-1}): 3141 (–NH–), 3023 (Ar-CH), 2935 (Aliph. CH), 1598 (C=N), 1574 (CH=CH), 1231, 1156 (=C–O–C); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 3.81 (s, 12H,

O–CH_3), 4.42 (s, 4H, O–CH_2), 5.92 (s, 2H, CH=CH), 7.30 (s, 2H, thiazole H), Ar-H [6.96 (s, 4H)], thiazole-Ph [7.39 (bs, 6H), 7.83 (s, 4H)], 7.94 (s, 2H, CH=N), 12.15 (s, 2H, –NH); ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 56.36 (O–CH_3), 72.58 (O–CH_2), thiazole-C [103.97 (CH), 141.86 (C), 168.85 (C)], Ar-C [107.94 (CH), 129.05 (C), 142.36 (C), 161.99 (C)], thiazole-Ph [125.94 (CH), 130.24 (CH), 131.74 (CH), 137.73 (C)], 129.43 (CH=CH), 153.77 (CH=N). MS: *m/z* 762.04 (M^+, 100). *Anal*. Calcd. for $C_{40}H_{38}N_6O_6S_2$: C, 62.97; H, 5.02; N, 11.02. Found: C, 63.00; H, 5.08; N, 11.04.

***(E)*-1,4-Bis(4-((*E*)-(2-(4-(4-bromophenyl)thiazol-2-yl)hydrazono)methyl)-2,6-dimethoxyphenoxy)but-2-ene (8b).** This compound was obtained as a light brown solid, yield 0.64 g (70%), mp 218°C (decomp.) (from DMF-EtOH, 2:1); IR (ATR, cm^{-1}): 3176 (–NH–), 3083 (Ar-CH), 2935 (Aliph. CH), 1593 (C=N), 1574 (CH=CH), 1227, 1123 (=C–O–C); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 3.81 (s, 12H, O–CH_3), 4.42 (s, 4H, O–CH_2), 5.92 (s, 2H, CH=CH), 7.37 (s, 2H, thiazole H), Ar-H [6.96 (s, 4H)], thiazole-Ph [7.57 (d, J = 8.4 Hz, 4H), 7.78 (d, J = 8.4 Hz, 4H)], 7.94 (d, J = 5.2 Hz, 2H, CH=N), 12.16 (s, 2H,–NH–); ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 56.35 (O–CH_3), 72.57 (O–CH_2), thiazole-C [104.00 (CH), 141.76 (C), 168.84 (C)], Ar-C [104.97 (CH), 127.96 (C), 137.76 (C), 162.75 (C)], thiazole-Ph [120.93 (C), 130.38 (CH), 131.98 (C), 134.36 (CH)], 129.44 (CH=CH), 153.76 (CH=N). MS: *m/z* 921.36 (M^+ + 1, 100). *Anal*. Calcd. for $C_{40}H_{36}Br_2N_6O_6S_2$: C, 52.18; H, 3.94; N, 9.13. Found: C, 52.26; H, 3.97; N, 9.06.

***(E)*-1,4-Bis(4-((*E*)-(2-(4-(4-chlorophenyl)thiazol-2-yl)hydrazono)methyl)-2,6-dimeth-oxyphenoxy)but-2-ene (8c).** This compound was obtained as an orange solid, yield 0.64 g (77%), mp 228–230°C (from DMF-EtOH, 2:1); IR (ATR, cm^{-1}): 3182 (–NH–), 3111 (Ar-CH), 2936 (Aliph. CH), 1606 (C=N), 1574 (CH=CH), 1226, 1123 (=C–O–C); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 3.81 (s, 12H, O–CH_3), 4.42 (s, 4H, O–CH_2), 5.91 (s, 2H, CH=CH), 7.36 (s, 2H, thiazole H), Ar-H [6.96 (s, 4H)], thiazole-Ph [7.44 (d, J = 8.8 Hz, 4H), 7.85 (d, J = 8.8 Hz, 4H)], 7.94 (d, J = 5.2 Hz, 2H, CH=N), 12.16 (s, 2H, –NH); ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 56.35 (O–CH_3), 72.14 (O–CH_2), thiazole-C [104.00 (CH), 141.73 (C), 168.83 (C)], Ar-C [104.89 (CH), 127.65 (C), 137.76 (C), 162.75 (C)], thiazole-Ph [129.07 (CH), 130.39 (CH), 132.34 (C), 134.04 (C)], 129.44 (CH=CH), 153.76 (CH=N). MS: *m/z* 832.53 (M^+ + 1, 100). *Anal*. Calcd. for $C_{40}H_{36}Cl_2N_6O_6S_2$: C, 57.76; H, 4.36; N, 10.10. Found: C, 57.74; H, 4.39; N, 10.04.

***(E)*-1,4-Bis(2,6-dimethoxy-4-((*E*)-(2-(4-(4-methoxyphenyl)thiazol-2-yl)hydrazono)methyl)phenoxy)but-2-ene (8d).** This compound was obtained as a yellowish brown solid, yield 0.48 g (58%), mp 182–184°C (from DMF-EtOH, 1:6); IR (ATR, cm^{-1}): 3132 (–NH–), 3045 (Ar-CH), 2936 (Aliph. CH), 1624 (C=N), 1574 (CH=CH), 1249, 1123 (=C–O–C); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 3.81 (s, 18H, O–CH_3), 4.41 (s, 4H, O–CH_2), 5.92 (s, 2H, CH=CH), 7.11 (s, 2H, thiazole H), Ar-H [6.95 (s, 4H)], thiazole-Ph [6.94 (d, J = 8.8 Hz, 4H), 7.76 (d, J = 8.8 Hz, 4H)], 7.94 (s, 2H, CH=N), 12.09 (s, 2H, –NH); ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 56.38 (O–CH_3), 72.55 (O–CH_2), thiazole-C [104.04 (CH), 141.57 (C), 168.89 (C)], Ar-C [106.17 (CH), 128.74 (C), 143.34 (C), 162.52 (C)], thiazole-Ph [114.40 (CH), 126.45 (C), 131.58 (CH), 157.12 (C)], 129.34 (CH=CH), 152.79 (CH=N). MS: *m/z* 823.92 (M^+ + 1, 100). *Anal*. Calcd. for $C_{42}H_{42}N_6O_8S_2$: C, 61.30; H, 5.14; N, 10.21. Found: C, 61.28; H, 5.18; N, 10.19.

***(E)*-1,4-Bis(4-((*E*)-(2-(4-([1,1'-biphenyl]-4-yl)thiazol-2-yl)hydrazono)methyl)-2,6-dimeth-oxyphenoxy)but-2-ene (8e).** This compound was obtained as an orange solid, yield 0.82 g (90%), mp 219–220°C (from DMF-EtOH, 2:1); IR (ATR, cm^{-1}): 3105 (–NH–), 3028 (Ar-CH), 2936 (Aliph. CH), 1625 (C=N), 1557 (CH=CH), 1228, 1116 (=C–O–C); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 3.82 (s, 12H, O–CH_3), 4.42 (s, 4H, O–CH_2), 5.92 (s, 2H, CH=CH), 7.36 (m, 2H, thiazole H), Ar-H [6.97 (s, 4H)], thiazole-Ph [7.70 (d, J = 8.4 Hz, 4H), 7.93 (d, J = 8.0 Hz, 4H)], Ph-Ph [7.35 (m, 2H), 7.47 (t, J = 7.6 Hz, 4H), 7.70 (d, J = 8.4 Hz, 4H)], 7.96 (s, 2H, CH=N), 12.17 (s, 2H, –NH); ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 56.37 (O–CH_3), 72.58 (O–CH_2), thiazole-C [104.00 (CH), 141.58 (C), 168.73 (C)], Ar-C [104.33 (CH), 127.91 (C), 137.73 (C), 162.94 (C)], thiazole-Ph [126.52 (CH), 127.92 (CH), 130.46 (C), 139.47 (C)], Ph-Ph [126.92 (CH), 127.28 (CH), 132.07 (CH), 140.10 (C)], 129.42 (CH=CH), 153.77 (CH=N). MS: *m/z* 916.25 (M^+ + 1, 100). *Anal*. Calcd. for $C_{52}H_{46}N_6O_6S_2$: C, 68.25; H, 5.07; N, 9.18. Found: C, 68.22; H, 5.11; N, 9.21.

***(E)*-1,4-Bis(2,6-dimethoxy-4-((*E*)-(2-(4-(4-nitrophenyl)thiazol-2-yl)hydrazono)methyl)-phenoxy)but-2-ene (8f).** This compound was obtained as an orange solid, yield 0.80 g (94%), mp 238–240°C (from DMF-EtOH, 1:1); IR (ATR, cm^{-1}): 3178 (–NH–), 3107 (Ar-CH), 2937 (Aliph. CH), 1601 (C=N), 1575 (CH=CH), 1233, 1109 (=C–O–C); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 3.81 (s, 12H, O–CH_3), 4.42 (s, 4H, O–CH_2), 5.92 (s, 2H, CH=CH), 7.69 (s, 2H, thiazole H), Ar-H [6.97 (s, 4H)], thiazole-Ph [8.09 (d, J = 8.8 Hz, 4H), 8.25 (d, J = 8.8 Hz, 4H)], 7.96 (s, 2H, CH=N), 12.26 (s, 2H, –NH); ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 56.36 (O–CH_3), 72.56 (O–CH_2), thiazole-C [104.07 (CH), 142.11 (C), 169.12 (C)], Ar-C [109.01 (CH), 130.28 (C), 146.64 (C), 162.75 (C)], thiazole-Ph [124.56 (CH), 126.76 (CH), 137.81 (C), 148.99 (C)], 129.46 (CH=CH), 153.77 (CH=N). MS: *m/z* 853.11 (M^+ + 1, 100). *Anal*. Calcd. for $C_{40}H_{36}N_8O_{10}S_2$: C, 56.33; H, 4.25; N, 13.14. Found: C, 56.29; H, 4.30; N, 13.16.

***(E)*-1,4-Bis(2,6-dimethyl-4-((*E*)-(2-(4-phenylthiazol-2-yl)hydrazono)methyl)phenoxy)but-2-ene (9a).** This compound was obtained as a yellow solid, yield 0.34 g (49%), mp 227–229°C (from DMF-

EtOH, 1:2); IR (ATR, cm^{-1}): 3136 (–NH–), 3047 (Ar-CH), 2924 (Aliph. CH), 1598 (C=N), 1558 (CH=CH), 1214, 1150 (=C–O–C); ^1H NMR (400 MHz, DMSO-d_6, δ ppm): 2.43 (s, 12H, CH_3), 4.56 (s, 4H, O–CH_2), 6.30 (s, 2H, CH=CH), 7.46 (s, 2H, thiazole H), Ar-H [7.49 (bs, 4H)], thiazole-Ph [7.57 (t, J = 7.6 Hz, 6H), 8.02 (s, 4H)], 8.11 (s, 2H, CH=N), 12.22 (s, 2H, –NH); ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 16.66 (CH_3), 72.14 (O–CH_2), thiazole-C [103.93 (CH), 141.56 (C), 168.68 (C)], Ar-C [125.95 (CH), 127.16 (C), 127.94 (C), 157.00 (C)], thiazole-Ph [129.06 (CH), 130.30 (CH), 131.59 (CH), 135.18 (C)], 129.22 (CH=CH), 150.77 (CH=N). MS: *m/z* 699.76 (M^+ + 1, 100). *Anal*. Calcd. for $C_{40}H_{38}N_6O_2S_2$: C, 68.74; H, 5.48; N, 12.02. Found: C, 68.77; H, 5.45; N, 12.08.

***(E)*-,4-Bis(4-((*E*)-(2-(4-(4-bromophenyl)thiazol-2-yl)hydrazono) methyl)-2,6-dimethyl-phenoxy)but-2-ene (9b).** This compound was obtained as a yellow solid, yield 0.43 g (50%), mp 252°C (decomp.) (from DMF-EtOH, 1:1); IR (ATR, cm^{-1}): 3168 (–NH–), 3071 (Ar-CH), 2917 (Aliph. CH), 1606 (C=N), 1574 (CH=CH), 1226, 1148 (=C–O–C); ^1H NMR (400 MHz, DMSO-d_6, δ ppm): 2.35 (s, 12H, CH_3), 4.47 (s, 4H, O–CH_2), 6.22 (s, 2H, CH=CH), 7.47 (s, 2H, thiazole H), Ar-H [7.41 (s, 4H)], thiazole-Ph [7.68 (d, J = 8.0 Hz, 4H), 7.89 (d, J = 8.0 Hz, 4H)], 8.03 (s, 2H, CH=N), 12.15 (s, 2H, –NH); ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 16.65 (CH_3), 72.14 (O–CH_2), thiazole-C [104.86 (CH), 141.76 (C), 168.83 (C)], Ar-C [127.19 (CH), 127.97 (C), 130.24 (C), 162.75 (C)], thiazole-Ph [120.92 (C), 131.61 (CH), 131.97 (C), 132.16 (CH)], 129.22 (CH=CH), 157.04 (CH=N). MS: *m/z* 857.83 (M^+ + 1, 100). *Anal*. Calcd. for $C_{40}H_{36}Br_2N_6O_2S_2$: C, 56.08; H, 4.24; N, 9.81. Found: C, 56.12; H, 4.31; N, 9.89.

***(E)*-1,4-Bis(4-((*E*)-(2-(4-(4-chlorophenyl)thiazol-2-yl)hydrazono) methyl)-2,6-dimethyl-phenoxy)but-2-ene (9c).** This compound was obtained as a yellow solid, yield 0.41 g (54%), mp 238–240°C (from DMF-EtOH, 1:2); IR (ATR, cm^{-1}): 3176 (–NH–), 3074 (Ar-CH), 2920 (Aliph. CH), 1603 (C=N), 1567 (CH=CH), 1289, 1148 (=C–O–C); ^1H NMR (400 MHz, DMSO-d_6, δ ppm): 2.42 (s, 12H, CH_3), 4.55 (s, 4H, O–CH_2), 6.29 (s, 2H, CH=CH), 7.52 (s, 2H, thiazole H), Ar-H [7.49 (s, 4H)], thiazole-Ph [7.62 (d, J = 6.8 Hz, 4H), 8.11 (d, J = 7.6 Hz, 4H)], 8.11 (s, 2H, CH=N), 12.22 (s, 2H, –NH); ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 16.65 (CH_3), 72.14 (O–CH_2), thiazole-C [104.75 (CH), 141.78 (C), 168.83 (C)], Ar-C [127.19 (CH), 127.66 (C), 129.06 (C), 162.75 (C)], thiazole-Ph [130.25 (CH), 131.60 (CH), 132.34 (C), 134.03 (C)], 129.22 (CH=CH), 157.04 (CH=N). MS: *m/z* 768.84 (M^+ + 1, 100). *Anal*. Calcd. for $C_{40}H_{36}Cl_2N_6O_2S_2$: C, 62.57; H, 4.73; N, 10.95. Found: C, 62.62; H, 4.75; N, 11.01.

***(E)*-1,4-Bis(4-((*E*)-(2-(4-(4-methoxyphenyl)thiazol-2-yl)hydrazono) methyl)-2,6-dimethyl-phenoxy)but-2-ene (9d).** This compound was obtained as an orange solid, yield 0.42 g (55%), mp 245°C (decomp.) (from DMF-EtOH, 1:2); IR (ATR, cm^{-1}): 3138 (–NH–), 3034 (Ar-CH), 2925 (Aliph. CH), 1609 (C=N), 1558 (CH=CH), 1251, 1148 (=C–O–C); ^1H NMR (400 MHz, DMSO-d_6, δ ppm): 2.38 (s, 12H, CH_3), 3.90 (s, 6H, O–CH_3), 4.51 (s, 4H, O–CH_2), 6.25 (s, 2H, CH=CH), 7.24 (s, 2H, thiazole H), Ar-H [7.44 (s, 4H)], thiazole-Ph [7.08 (d, J = 8.4 Hz, 4H), 7.89 (d, J = 8.4 Hz, 4H)], 8.05 (s, 2H, CH=N), 12.13 (s, 2H, –NH); ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 16.65 (CH_3), 55.56 (O–CH_3), 72.14 (O–CH_2), thiazole-C [101.76 (CH), 141.43 (C), 168.57 (C)], Ar-C [127.14 (CH), 128.07 (C), 130.34 (C), 162.75 (C)], thiazole-Ph [114.40 (CH), 127.27 (C), 131.58 (CH), 156.96 (C)], 129.22 (CH=CH), 150.82 (CH=N). MS: *m/z* 759.97 (M^+ + 1, 100). *Anal*. Calcd. for $C_{42}H_{42}N_6O_4S_2$: C, 66.47; H, 5.58; N, 11.07. Found: C, 66.51; H, 5.60; N, 11.11.

***(E)*-1,4-Bis(4-((*E*)-(2-(4-([1,1'-biphenyl]-4-yl)thiazol-2-yl)hydrazono) methyl)-2,6-dimethyl-phenoxy)but-2-ene (9e).** This compound was obtained as a light brown solid, yield 0.52 g (60%), mp 252°C (decomp.) (from DMF-EtOH, 1:2); IR (ATR, cm^{-1}): 3139 (–NH–), 3031 (Ar-CH), 2924 (Aliph. CH), 1599 (C=N), 1558 (CH=CH), 1214, 1126 (=C–O–C); ^1H NMR (400 MHz, DMSO-d_6, δ ppm): 2.27 (s, 12H, CH_3), 4.40 (s, 4H, O–CH_2), 6.13 (s, 2H, CH=CH), 7.34 (s, 2H, thiazole H), Ar-H [7.70 (s, 4H)], thiazole-Ph [7.71 (d, J = 8.4 Hz, 4H), 7.95 (d, J = 8.4 Hz, 4H)], Ph-Ph [7.38 (m, 6H), 7.47 (t, J = 7.6 Hz, 4H)], 7.96 (s, 2H, CH=N), 12.08 (s, 2H, –NH); ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 16.66 (CH_3), 72.13 (O–CH_2), thiazole-C [104.15 (CH), 141.66 (C), 168.75 (C)], Ar-C [126.53 (CH), 127.18 (C), 127.91 (C), 162.74 (C)], thiazole-Ph [127.26 (CH), 129.21 (CH), 134.29 (C), 157.01 (C)], Ph-Ph [130.31 (CH), 131.59 (CH), 139.46 (CH), 140.10 (C)], 129.41 (CH=CH), 150.62 (CH=N). MS: *m/z* 851.32 (M^+, 100). *Anal*. Calcd. for $C_{52}H_{46}N_6O_2S_2$: C, 73.38; H, 5.45; N, 9.87. Found: C, 73.41; H, 5.50; N, 9.90.

***(E)*-1,4-Bis(2,6-dimethyl-4-((*E*)-(2-(4-(4-nitrophenyl)thiazol-2-yl) hydrazono)methyl)-phenoxy)but-2-ene (9f).** This compound was obtained as a light brown solid, yield 0.73 g (92%), mp 256°C (decomp.) (from DMF-EtOH, 1:1); IR (ATR, cm^{-1}): 3188 (–NH–), 3087 (Ar-CH), 2924 (Aliph. CH), 1596 (C=N), 1573 (CH=CH), 1209, 1150 (=C–O–C); ^1H NMR (400 MHz, DMSO-d_6, δ ppm): 2.38 (s, 12H, CH_3), 4.51 (s, 4H, O–CH_2), 6.25 (s, 2H, CH=CH), 7.82 (s, 2H, thiazole H), Ar-H [7.45 (s, 4H)], thiazole-Ph [8.22 (d, J = 8.4 Hz, 4H), 8.39 (d, J = 8.0 Hz, 4H)], 8.07 (d, J = 4.4 Hz, 2H, CH=N), 12.29 (s, 2H, –NH); ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 16.66 (CH_3), 72.14 (O–CH_2), thiazole-C [108.88 (CH), 141.82 (C), 169.12 (C)], Ar-C [126.78 (CH), 127.26 (C), 131.63 (C), 162.76 (C)], thiazole-Ph [124.56 (CH), 130.14 (CH), 146.65 (C), 157.12 (C)], 129.23 (CH=CH), 148.98 (CH=N). MS: *m/z* 789.77 (M^+ + 1, 100). *Anal*. Calcd. for $C_{40}H_{36}N_8O_6S_2$: C, 60.90; H, 4.60; N, 14.20. Found: C, 60.94; H, 4.57; N, 14.15.

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