Synthesis, S-alkylation, and fungicidal activity of 4-(benzylideneamino)thioglycolurils

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A series of 1,3-disubstituted 4-benzylideneamino-5-thioxohexahydroimidazo[4,5-*d*]imidazol-2(1*H*)-ones (thioglycolurils) was synthesized *via* the reaction of 5,7-disubstituted 3-thioxoperhydroimidazo[4,5-*e*]-1,2,4-triazin-6-ones with hydroxy-, alkoxy-, and fluoro-containing benzaldehyde derivatives. An alkylation of the obtained thioglycolurils with methyl iodide or 4-bromobenzyl bromide provided the corresponding 6-benzylideneamino-5-alkylsulfanyl-3,3a,6,6a-tetrahydroimidazo[4,5-*d*]imidazol-2(1*H*)-ones. The fungicidal activity of some synthesized compounds against pathogens causing diseases of agricultural crops was studied.

Key words: 3-thioxoperhydroimidazo[4,5-*e*]-1,2,4-triazin-6-ones, ring contraction, 5-thioxohexahydroimidazo[4,5-*d*]imidazol-2(1*H*)-ones, thioglycolurils, S-alkylation, Triadimefon, fungicidal activity.

Imidazolidine-2-thione derivatives attract an attention of researchers due to their various biological activity and ability to form complexes with transition metal salts.[1—16]. Thiohydantoins (2-thioxoimidazolidin-4-ones) exhibit antiproliferative,[1—3] fungicidal, and antibacterial activities[3,4] and inhibit the mutant isocitrate dehydrogenase, which is stimulating carcinogenesis.[5] Thioglycolurils (5-thioxohexahydroimidazo[4,5-*d*]imidazol-2(1*H*)-ones) cause the sedative,[6] fungicidal and cytotoxic effects.[7,8] Alkylsulfanyl derivatives of thiohydantoins and thioglycolurils inhibit the mycelial growth of phytopathogenic fungi, while 4-methyl-2-methylsulfanyl-4-phenyl-1-phenylamino-1*H*-imidazol-5(4*H*)-one so-called Fenamidon is used as a fungicidal agent for the agricultural crop protection.[8—10]

This work was aimed at the synthesis of 4-(benzylideneamino)thioglycolurils and their S-alkyl derivatives and at the investigation of the fungicidal activity of the prepared compounds. Thioglycolurils **1a—l** were synthesized according to our method developed previously[17] *via* a tandem reaction including the hydrazone formation and triazine ring contraction of imidazotriazines **2a—c** with hydroxy-, alkoxy- and fluoro-substituted benzaldehydes **3a—j** (Scheme 1).

The previous X-ray diffraction studies of single crystals of thioglycolurils prepared *via* the reaction of triazine ring contraction caused by aldehydes revealed that all the studied compounds, including compound **1i**, possess the *E*-configuration of the C=N bond.[7,8,17—19]

S-Alkyl derivatives **4** were obtained by the alkylation of thioglycolurils **1** with methyl iodide or 4-bromobenzyl bromide in the presence of potassium carbonate (Scheme 2).

The reaction with methyl iodide was carried out in methanol under heating at 60 °C, while that with 4-bromobenzyl bromide was performed in dimethylsulfoxide at room temperature. However, the alkylation of thioglycoluril **1c** with 4-bromobenzyl bromide provided also both O- and S-alkylation product **4j** (the yield of 23% based on 4-bromobenzyl bromide) in addition to desired S-alkyl derivative **4i** (52% yield).

The IR spectra of alkylsulfanyl derivatives **4** did not contain an absorption band of the NH group in the region of 3160—3243 cm^{-1} as compared to the spectra of thioglycolurils **1**. In the ^1H NMR spectra of compounds **4**, the singlet signals from the proton in the NH group (δ = = 9.85—10.26) disappeared, while the signals arise as the singlets from protons in the SMe at δ = 2.42—2.45 and SCH_2 at δ = 4.26—4.29 groups, and as the two doublets of aromatic protons in the 4-bromobenzyl moiety at δ = = 7.40—7.52. The ^{13}C NMR spectra did not contain a signal from the C=S group in the region of δ = 178.4—179.7 and contained the signals from the N=C—S, SMe, or

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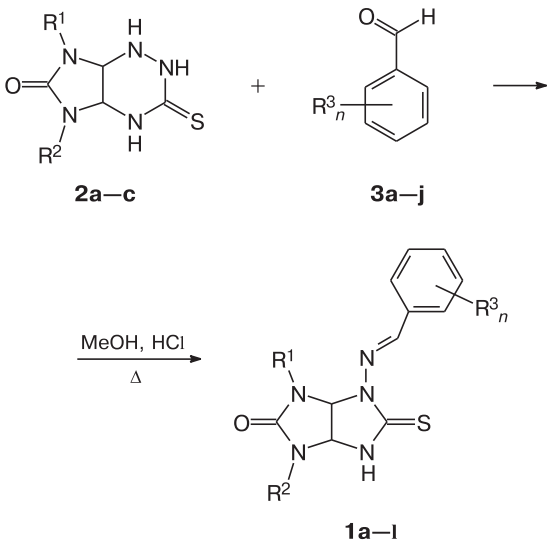
Scheme 1



2a—c **3a—j**

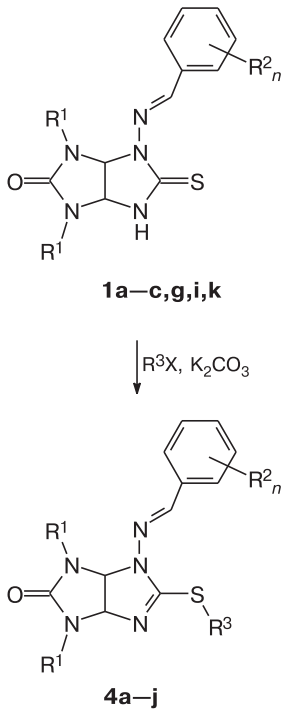
1a—l

Starting Compounds	R^1	R^2	$R^3{}_n$	Product	Yield (%)
2a, **3a**	Me	Me	2-F	**1a**	47
2a, **3b**	Me	Me	3-MeO	**1b**	48
2a, **3c**	Me	Me	2-HO-3-MeO	**1c**	60
2a, **3d**	Me	Me	2-HO-5-Me	**1d**	47
2a, **3e**	Me	Me	4-HO-3-MeO	**1e**	44
2a, **3f**	Me	Me	4-BnO-3-MeO	**1f**	49
2b, **3a**	Et	Et	2-F	**1g**	45
2b, **3g**	Et	Et	4-F	**1h**	69
2b, **3h**	Et	Et	4-MeO	**1i**	65
2b, **3i**	Et	Et	4-F_3C	**1j**	34
2b, **3j**	Et	Et	4-EtO-3-MeO	**1k**	59
2c, **3e**	Me	Ph	4-HO-3-MeO	**1l**	44

SCH_2 groups at δ = 165.3—166.8, 12.9—13.0, and 33.1, respectively.

Since the (phenylallylidenamino)thioglycolurils and their S-alkyl derivatives obtained earlier by us demonstrated the fungicidal effect on the causative agents of rhizoctoniose and fusariose, *Rhizoctonia solani*, *Fusarium oxysporum*, and *Fusarium moniliforme*;[8] some of synthesized compounds **1** and **4** were tested for the fungicidal activity *in vitro* according to the known method[20,21] in comparison with Triadimefon as the standard against the six species of phytopathogenic fungi belonging to the different taxonomic classes: *Venturia inaequalis* (*V.i.*) is the causative agent of apple scab, *Rhizoctonia solani* (*R.s.*) is the causative agent of rhizoctoniose, *Fusarium oxysporum* (*F.o.*) and *Fusarium moniliforme* (*F.m.*) are the causative agents of fusariose, *Bipolaris sorokiniana* (*B.s.*) is the causative agent of root rot, and *Sclerotinia sclerotiorum* (*S.s.*) is the causative agent of white rot. However, the tested compounds demonstrated a little or no activity against *Venturia inaequalis, Fusarium oxysporum, Bipolaris sorokiniana*, and *Sclerotinia sclerotiorum*. Their most noticeable effect was

Scheme 2



1a—c,g,i,k

4a—j

X = I, Br

Product	R^1	$R^2{}_n$	R^3	Yield (%)
4a	Me	2-F	Me	95
4b	Me	3-MeO	Me	81
4c	Me	2-HO-3-MeO	Me	79
4d	Et	2-F	Me	86
4e	Et	4-MeO	Me	76
4f	Et	4-EtO-3-MeO	Me	75
4g	Me	2-F	4-$BrC_6H_4CH_2$	91
4h	Me	3-MeO	4-$BrC_6H_4CH_2$	84
4i	Me	2-HO-3-MeO	4-$BrC_6H_4CH_2$	52
4j	Me	2-(4-$BrC_6H_4CH_2O$)-3-MeO	4-$BrC_6H_4CH_2$	23

on the mycelial growth of *Rhizoctonia solani* (*R.s.*) and *Fusarium moniliforme* (*F.m.*), but the activity of all the investigated thioglycolurils did not exceed that of the Triadimefon reference (Table 1). The close to Triadimefon level of suppression of mycelial growth of *Rhizoctonia solani* was demonstrated by methylsulfanyl derivative **4e**.

Therefore, (benzylideneamino)thioglycolurils were synthesized *via* the tandem reaction including the hydrazone formation and triazine ring contraction of imidazotriazines with the substituted benzaldehydes. The alkylation of these thioglycolurils with methyl iodide or 4-bromobenzyl bromide provided their S-alkyl derivatives in the yields of 75—95%. The obtained compounds demonstrated the significantly weaker fungicidal activity in comparison with the (phenylallylidenamino)thioglycolurils and their S-alkyl derivatives previously studied by us.

Table 1. The fungicidal activity of synthesized compounds *in vitro* (c = 30 mg L^{-1})

Compound	Mycelial growth inhibition (%)	
	R.s.	*F.m.*
1a	10	20
1c	38	11
1e	16	23
1f	31	22
1g	18	24
1i	19	40
1j	23	17
1k	30	19
4e	47	16
4g	19	15
Triadimefon*	52	61

*Triadimefon is 3,3-dimethyl-1-(1,2,4-triazol-1-yl)-1-(4-chlorophenoxy)butan-2-one.

Experimental

The NMR spectra were recorded on a Bruker AM-300 spectrometer (^{1}H, 300.13 MHz; ^{13}C, 75.5 MHz; and ^{19}F, 282 MHz) in DMSO-d_6, the chemical shifts are reported as δ values relative to Me_4Si or $CFCl_3$ used as the internal standards. High-resolution mass spectra (HRMS) were recorded on a Bruker micrOTOF II instrument using electrospray ionization (ESI). The measurements were performed in a positive ion mode (the interface capillary voltage of 4500 V). The mass range interval was from m/z 50 to 3000 Da using an external or internal calibration (Electrospray Calibrant Solution, Fluka). A syringe injection was used for solutions in MeCN or MeOH; the flow rate was 3 μL min^{-1}; N_2 was used as the nebulizer gas (4 L min^{-1}); the interface temperature was set at 180 °C. The melting points of compounds were determined on a Boetius microblock.

Synthesis of 1,3-disubstituted 4-benzylideneamino-5-thioxohexahydroimidazo[4,5-*d*]imidazol-2(1*H*)-ones 1a—l (general procedure). Aldehyde **3a—j** (2.1 mmol) and HCl (conc., 2 drops) were added to a suspension of imidazotriazine **2a—c** (2 mmol) in MeOH (30 mL). The resulting mixture was refluxed under stirring for 1.5 h, cooled, and kept at room temperature for 4—48 h. The formed precipitate was isolated by filtration, wased with methanol, and dried in air.

(*E*)-4-[(2-Fluorobenzylidene)amino]-1,3-dimethyl-5-thioxohexahydroimidazo[4,5-*d*]imidazol-2(1*H*)-one (1a). The yield was 47%; white crystals, m.p. 189—191 °C (dec.). IR (KBr), ν/cm^{-1}: 3179 (NH), 1698 (C=O), 1610 (C=N), 1519, 1493, 1419, 1233, 1046. ^{1}H NMR, δ: 2.76 (s, 3 H, NMe); 2.88 (s, 3 H, NMe); 5.41 (d, 1 H, CH, J = 8.3 Hz); 6.01 (d, 1 H, CH, J = 8.3 Hz); 7.29—7.35 (m, 2 H, 3,5-ArH); 7.49—7.56 (m, 1 H, 4-ArH); 7.93 (t, 1 H, 6-ArH, J = 7.5 Hz); 9.45 (s, 1 H, N=CH); 10.13 (s, 1 H, NH). ^{13}C NMR, δ: 28.1 (NMe); 30.2 (NMe); 68.0 (CH); 75.3 (CH); 116.1 (d, $^2J_{C,F}$ = 20.7 Hz); 121.5 (d, $^2J_{C,F}$ = 10.1 Hz); 125.0 (d, $J_{C,F}$ = 3.3 Hz); 126.4 (d, $J_{C,F}$ = 2.5 Hz); 132.5 (d, $J_{C,F}$ = 8.7 Hz); 143.1 (d, $J_{C,F}$ = 4.9 Hz); 157.5 (C=O); 160.9 (d, $^1J_{C,F}$ = 251.0 Hz); 178.7 (C=S). ^{19}F NMR, δ: −120.94. MS (ESI), m/z: $[M + Na]^+$; found: 330.0784; calculated for $C_{13}H_{14}FN_5OS$: 330.0795.

(*E*)-4-[(3-Methoxybenzylidene)amino]-1,3-dimethyl-5-thioxohexahydroimidazo[4,5-*d*]imidazol-2(1*H*)-one (1b). The yield was 48%, white crystals, m.p. 203—205 °C (dec.). The spectral characteristics corresponded to that reported earlier.[7]

(*E*)-4-[(2-Hydroxy-3-methoxybenzylidene)amino]-1,3-dimethyl-5-thioxohexahydroimidazo[4,5-*d*]imidazol-2(1*H*)-one (1c). The yield was 60%, white crystals, m.p. 221—223 °C (dec.). The spectral characteristics corresponded to that reported earlier.[17]

(*E*)-4-[(2-Hydroxy-5-methylbenzylidene)amino]-1,3-dimethyl-5-thioxohexahydroimidazo[4,5-*d*]imidazol-2(1*H*)-one (1d). The yield was 47%, white powder, m.p. 241—243 °C (dec.). IR (KBr), ν/cm^{-1}: 3407 (OH), 3173 (NH), 1720, 1678 (C=O), 1613 (C=N), 1526, 1492, 1415, 1269, 1201, 1044. ^{1}H NMR, δ: 2.24 (s, 3 H, Me); 2.77 (s, 3 H, NMe); 2.92 (s, 3 H, NMe); 5.48 (d, 1 H, CH, J = 8.2 Hz); 6.15 (d, 1 H, CH, J = 8.2 Hz); 6.83 (d, 1 H, ArH, J = 8.3 Hz); 7.13 (d, 1 H, ArH, J = 8.3 Hz); 7.36 (s, 1 H, ArH); 8.74 (s, 1 H, N=CH); 10.26 (s, 1 H, NH); 10.89 (s, 1 H, OH). ^{13}C NMR, δ: 20.0 (Me); 28.3 (NMe); 30.9 (NMe); 68.9 (CH); 72.2 (CH); 116.6; 118.0; 128.0; 130.1; 132.5; 147.7 (N=CH); 155.2; 157.6 (C=O); 179.7 (C=S). MS (ESI), m/z: $[M + Na]^+$; found: 342.1000; calculated for $C_{14}H_{17}N_5O_2S$: 342.0995.

(*E*)-4-[(4-Hydroxy-3-methoxybenzylidene)amino]-1,3-dimethyl-5-thioxohexahydroimidazo[4,5-*d*]imidazol-2(1*H*)-one (1e). The yield was 44%, white powder, m.p. 132—134 °C (dec.). IR (KBr), ν/cm^{-1}: 3436 (OH), 3160 (NH), 1703 (C=O), 1639, 1599 (C=C, C=N), 1510, 1457, 1426, 1269, 1251, 1223, 1042, 1032. ^{1}H NMR, δ: 2.76 (s, 3 H, NMe); 2.84 (s, 3 H, NMe); 3.82 (s, 3 H, OMe); 5.38 (d, 1 H, CH, J = 8.2 Hz); 5.89 (d, 1 H, CH, J = 8.2 Hz); 6.87 (d, 1 H, ArH, J = 8.3 Hz); 7.20 (d, 1 H, ArH, J = 8.3 Hz); 7.35 (s, 1 H, ArH); 8.97 (s, 1 H, N=CH); 9.71 (s, 1 H, OH); 9.87 (s, 1 H, NH). ^{13}C NMR, δ: 28.1 (NMe); 29.8 (NMe); 55.5 (OMe); 67.9 (CH); 75.7 (CH); 110.0; 115.5; 122.3; 125.0; 147.9; 149.6; 154.9 (N=CH); 157.5 (C=O); 178.7 (C=S). MS (ESI), m/z: $[M + Na]^+$; found: 358.0941; calculated for $C_{14}H_{17}N_5O_3S$: 358.0944.

(*E*)-4-[(4-Benzyloxy-3-methoxybenzylidene)amino]-1,3-dimethyl-5-thioxohexahydroimidazo[4,5-*d*]imidazol-2(1*H*)-one (1f). The yield was 49%, white powder, m.p. 212—214 °C (dec.). IR (KBr), ν/cm^{-1}: 3165 (NH), 1708 (C=O), 1599, 1575 (C=C, C=N), 1509, 1458, 1401, 1267, 1225, 1198, 1141. ^{1}H NMR, δ: 2.75 (s, 3 H, NMe); 2.84 (s, 3 H, NMe); 3.81 (s, 3 H, OMe); 5.15 (s, 2 H, OCH_2); 5.38 (d, 1 H, CH, J = 8.3 Hz); 5.91 (d, 1 H, CH, J = 8.2 Hz); 7.14 (d, 1 H, ArH, J = 8.4 Hz); 7.28 (d, 1 H, ArH, J = 8.4 Hz); 7.32—7.47 (m, 6 H, ArH); 9.03 (s, 1 H, N=CH); 9.91 (s, 1 H, NH). ^{13}C NMR, δ: 28.2 (NMe); 30.0 (NMe); 55.5 (OMe); 69.0 (OCH_2); 69.9 (CH); 75.5 (CH); 109.3; 113.2; 121.9; 126.7; 127.9 (2 C); 128.0; 128.4 (2 C); 136.7; 149.3; 150.2; 153.6 (N=CH); 157.6 (C=O); 178.8 (C=S). MS (ESI), m/z: $[M + Na]^+$; found: 448.1411; calculated for $C_{21}H_{23}N_5O_3S$: 448.1414.

(*E*)-1,3-Diethyl-4-[(2-fluorobenzylidene)amino]-5-thioxohexahydroimidazo[4,5-*d*]imidazol-2(1*H*)-one (1g). The yield was 45%, white crystals, m.p. 234—236 °C (dec.). IR (KBr), ν/cm^{-1}: 3199 (NH), 1687 (C=O), 1606 (C=N), 1509, 1482, 1451, 1276, 1252, 1238, 1206. ^{1}H NMR, δ: 1.04—1.10 (m, 6 H, Me); 3.09—3.43 (m, 4 H, NCH_2); 5.52 (d, 1 H, CH, J = 8.3 Hz); 6.04 (d, 1 H, CH, J = 8.3 Hz); 7.30—7.35 (m, 2 H, 3,5-ArH); 7.50—7.57 (m, 1 H, 4-ArH); 7.91 (t, 1 H, 6-ArH, J = 7.4 Hz); 9.60 (s, 1 H, N=CH); 10.10 (s, 1 H, NH). ^{13}C NMR, δ: 12.9

(Me); 13.3 (Me); 35.9 (NCH_2); 37.2 (NCH_2); 66.2 (CH); 74.5 (CH); 116.2 (d, $^2J_{C,F}$ = 20.7 Hz); 121.4 (d, $^2J_{C,F}$ = 9.9 Hz); 125.1 (d, $J_{C,F}$ = 3.2 Hz); 126.3 (d, $J_{C,F}$ = 2.2 Hz); 132.7 (d, $J_{C,F}$ = = 8.6 Hz); 144.5 (d, $J_{C,F}$ = 4.5 Hz); 156.8 (C=O); 160.9 (d, $^1J_{C,F}$ = 251.2 Hz); 178.4 (C=S). ^{19}F NMR, δ: –120.90. MS (ESI), *m/z*: $[M + Na]^+$; found: 358.1096; calculated for $C_{15}H_{18}FN_5OS$: 358.1108.

(*E*)-1,3-Diethyl-4-[(4-fluorobenzylidene)amino]-5-thioxohexahydroimidazo[4,5-*d*]imidazol-2(1*H*)-one (1h). The yield was 69%, white crystals, m.p. 208—210 °C (dec.). IR (KBr), ν/cm^{-1}: 3199 (NH), 1680 (C=O), 1601 (C=N), 1509, 1477, 1450, 1267, 1251, 1227, 1191. ^{1}H NMR, δ: 1.01—1.10 (m, 6 H, Me); 3.11—3.40 (m, 4 H, NCH_2); 5.51 (d, 1 H, CH, *J* = 8.4 Hz); 5.97 (d, 1 H, CH, *J* = 8.4 Hz); 7.33 (t, 2 H, ArH, *J* = 8.7 Hz); 7.82 (dd, 2 H, ArH, *J* = 8.3 Hz, *J* = 5.8 Hz); 9.25 (s, 1 H, N=CH); 9.97 (s, 1 H, NH). ^{13}C NMR, δ: 12.9 (Me); 13.4 (Me); 35.9 (NCH_2); 37.1 (NCH_2); 66.2 (CH); 74.7 (CH); 116.0 (d, 2 C, $^2J_{C,F}$ = 22.0 Hz); 129.6 (d, 2 C, $^3J_{C,F}$ = 8.8 Hz); 130.3 (d, $^4J_{C,F}$ = = 3.0 Hz); 152.8 (C=N); 156.8 (C=O); 163.6 (d, $^1J_{C,F}$ = 248.9 Hz); 178.7 (C=S). ^{19}F NMR, δ: –110.22. MS (ESI), *m/z*: $[M + Na]^+$; found: 358.1110; calculated for $C_{15}H_{18}FN_5OS$: 358.1108.

(*E*)-1,3-Diethyl-4-[(4-methoxybenzylidene)amino]-5-thioxohexahydroimidazo[4,5-*d*]imidazol-2(1*H*)-one (1i). The yield was 65%, white crystals, m.p. 208—210 °C (dec.). The spectral characteristics corresponded to that reported earlier.[6,7]

(*E*)-1,3-Diethyl-4-{[4-(trifluoromethyl)benzylidene]amino}-5-thioxohexahydroimidazo[4,5-*d*]imidazol-2(1*H*)-one (1j). The yield was 34%, white crystals, m.p. 212—213 °C (dec.). IR (KBr), ν/cm^{-1}: 3243 (NH), 1686, 1677 (C=O), 1618 (weak, C=N), 1501, 1480, 1324, 1254, 1235, 1166, 1127, 1066. ^{1}H NMR, δ: 1.01—1.11 (m, 6 H, Me); 3.10—3.45 (m, 4 H, NCH_2); 5.54 (d, 1 H, CH, *J* = 8.4 Hz); 6.05 (d, 1 H, CH, *J* = 8.3 Hz); 7.85 (d, 2 H, ArH, *J* = 8.0 Hz); 7.97 (d, 2 H, ArH, *J* = 8.0 Hz); 9.36 (s, 1 H, N=CH); 10.13 (s, 1 H, NH). ^{13}C NMR, δ: 13.0 (Me); 13.5 (Me); 36.0 (NCH_2); 37.4 (NCH_2); 66.4 (CH); 74.3 (CH); 124.1 (q, CF_3, $^1J_{C,F}$ = 272.4 Hz); 125.9 (q, 2 C, $^3J_{C,F}$ = 3.8 Hz); 128.0 (2 C); 130.3 (q, $^2J_{C,F}$ = 31.8 Hz); 137.9; 149.9 (C=N); 157.0 (C=O); 178.8 (C=S). ^{19}F NMR, δ: –62.05. MS (ESI), *m/z*: $[M + Na]^+$; found: 408.1061; calculated for $C_{16}H_{18}F_3N_5OS$: 408.1076.

(*E*)-4-[(4-Ethoxy-3-methoxybenzylidene)amino]-1,3-diethyl-5-thioxohexahydroimidazo[4,5-*d*]imidazol-2(1*H*)-one (1k). The yield was 59%, white powder, m.p. 197—199 °C (dec.). IR (KBr), ν/cm^{-1}: 3224 (NH), 1699, 1685 (C=O), 1602, 1571 (C=C, C=N), 1503, 1476, 1454, 1334, 1257, 1197, 1136, 1034. ^{1}H NMR, δ: 1.03—1.10 (m, 6 H, Me); 1.35 (t, 3 H, Me, *J* = 7.0 Hz); 3.11—3.41 (m, 4 H, NCH_2); 3.80 (s, 3 H, OMe); 4.07 (q, 2 H, OCH_2, *J* = 7.0 Hz); 5.48 (d, 1 H, CH, *J* = 8.5 Hz); 5.93 (d, 1 H, CH, *J* = 8.4 Hz); 7.04 (d, 1 H, ArH, *J* = 8.2 Hz); 7.26 (d, 1 H, ArH, *J* = 8.2 Hz); 7.36 (s, 1 H, ArH); 9.17 (s, 1 H, N=CH); 9.85 (s, 1 H, NH). ^{13}C NMR, δ: 12.9 (Me); 13.4 (Me); 14.6 (Me); 35.9 (NCH_2); 37.1 (NCH_2); 55.4 (OMe); 63.8 (OCH_2); 66.1 (CH); 75.1 (CH); 109.0; 112.4; 122.2; 126.1; 149.1; 150.6; 155.6 (N=CH); 156.9 (C=O); 178.5 (C=S). MS (ESI), *m/z*: $[M + Na]^+$; found: 414.1566; calculated for $C_{18}H_{25}N_5O_3S$: 414.1570.

(*E*)-4-[(4-Hydroxy-3-methoxybenzylidene)amino]-3-methyl-1-phenyl-5-thioxohexahydroimidazo[4,5-*d*]imidazol-2(1*H*)-one (1l). The yield was 44%, white powder, m.p. 224—226 °C (dec.). IR (KBr), ν/cm^{-1}: 3539 (OH), 3200 (NH), 1718, 1692 (C=O), 1597 (C=C, C=N), 1498, 1461, 1450, 1429, 1403, 1377, 1269, 1249, 1227, 1198, 1175, 1118, 1030. ^{1}H NMR, δ: 2.94 (s, 3 H, NMe); 3.83 (s, 3 H, OMe); 6.01 (d, 1 H, CH, *J* = 8.4 Hz); 6.15 (d, 1 H, CH, *J* = 8.5 Hz); 6.87 (d, 1 H, ArH, *J* = 8.2 Hz); 7.12 (t, 1 H, Ph, *J* = 7.3 Hz); 7.22 (d, 1 H, ArH, *J* = 8.2 Hz); 7.34—7.39 (m, 3 H, ArH, Ph); 7.59 (d, 2 H, Ph, *J* = 8.1 Hz); 9.09 (s, 1 H, N=CH); 9.68 (s, 1 H, OH); 10.05 (s, 1 H, NH). ^{13}C NMR, δ: 29.8 (NMe); 55.6 (OMe); 66.4 (CH); 75.5 (CH); 110.0; 115.6; 199.4 (2 C, Ph), 122.5; 123.5 (Ph); 124.9; 128.8 (2 C, Ph); 137.8 (Ph); 148.0; 149.8; 155.1 (C=O); 156.6 (N=CH); 179.2 (C=S). MS (ESI), *m/z*: $[M + Na]^+$; found: 420.1096; calculated for $C_{19}H_{19}N_5O_3S$: 420.1101.

Synthesis of methylsulfanyl derivatives 4a—f (general procedure). Methyl iodide (0.125 mL, 2 mmol) was added to a stirred suspension of thioglycoluril **1** (1 mmol) and potassium carbonate (0.138 g, 1 mmol) in MeOH (30 mL). The resulting mixture was stirred at 60 °C for 2 h and then concentrated *in vacuo*. The residue was resuspended with water; the formed precipitate was isolated by filtration, wased with water, and dried in air.

(*E*)-6-[(2-Fluorobenzylidene)amino]-1,3-dimethyl-5-methylsulfanyl-3,3a,6,6a-tetrahydroimidazo[4,5-*d*]imidazol-2(1*H*)-one (4a). The yield was 91%, white powder, m.p. 208—210 °C. IR (KBr), ν/cm^{-1}: 1718, 1563, 1488, 1404, 1282, 1215, 1039. ^{1}H NMR, δ: 2.44 (s, 3 H, SMe); 2.83 (s, 3 H, NMe); 2.92 (s, 3 H, NMe); 5.59 (d, 1 H, CH, *J* = 7.8 Hz); 6.03 (d, 1 H, CH, *J* = 7.9 Hz); 7.26—7.32 (m, 2 H, 3,5-ArH); 7.41—7.47 (m, 1 H, 4-ArH); 7.79 (t, 1 H, 6-ArH, *J* = 7.7 Hz); 8.16 (s, 1 H, N=CH). ^{13}C NMR, δ: 13.0 (SMe); 28.4 (NMe); 30.8 (NMe); 72.3 (CH); 79.9 (CH); 116.0 (d, $^2J_{C,F}$ = 20.6 Hz); 122.0 (d, $^2J_{C,F}$ = = 10.2 Hz); 124.9 (d, $J_{C,F}$ = 3.2 Hz); 126.0 (d, $J_{C,F}$ = 2.6 Hz); 130.8 (d, $J_{C,F}$ = 4.3 Hz); 131.3 (d, $J_{C,F}$ = 8.4 Hz); 157.7 (C=O); 160.3 (d, $^1J_{C,F}$ = 250.1 Hz); 166.6 (N=C—S). ^{19}F NMR, δ: –121.63. MS (ESI), *m/z*: $[M + Na]^+$; found: 344.0952; calculated for $C_{14}H_{16}FN_5OS$: 344.0952.

(*E*)-6-[(3-Methoxybenzylidene)amino]-1,3-dimethyl-5-methylsulfanyl-3,3a,6,6a-tetrahydroimidazo[4,5-*d*]imidazol-2(1*H*)-one (4b). The yield was 81%, white powder, m.p. 160—162 °C. IR (KBr), ν/cm^{-1}: 1715, 1603 (weak), 1562, 1489, 1450, 1426, 1398, 1285, 1272, 1210, 1186, 1156, 1048, 1033. ^{1}H NMR, δ: 2.43 (s, 3 H, SMe); 2.83 (s, 3 H, NMe); 2.91 (s, 3 H, NMe); 3.79 (s, 3 H, OMe); 5.59 (d, 1 H, CH, *J* = 7.7 Hz); 5.92 (d, 1 H, CH, *J* = 7.8 Hz); 6.96 (d, 1 H, ArH, *J* = 7.6 Hz); 7.24—7.28 (m, 2 H, ArH); 7.35 (t, 1 H, ArH, *J* = 7.7 Hz); 8.06 (s, 1 H, N=CH). ^{13}C NMR, δ: 12.9 (SMe); 28.3 (NMe); 30.5 (NMe); 55.1 (OMe); 72.2 (CH); 80.0 (CH); 111.4; 115.2; 119.0; 129.9; 135.9; 137.9 (N=CH); 157.6 (C=O); 159.5; 166.8 (N=C—S). MS (ESI), *m/z*: $[M + H]^+$; found: 334.1320; calculated for $C_{15}H_{19}N_5O_2S$: 334.1332.

(*E*)-6-[(2-Hydroxy-3-methoxybenzylidene)amino]-1,3-dimethyl-5-methylsulfanyl-3,3a,6,6a-tetrahydroimidazo[4,5-*d*]-imidazol-2(1*H*)-one (4c). The yield was 79%, white powder, m.p. 187—189 °C. IR (KBr), ν/cm^{-1}: 3301, 1704, 1606, 1579, 1566, 1480, 1444, 1403, 1267, 1213, 1193, 1066, 1036. ^{1}H NMR, δ: 2.45 (s, 3 H, SMe); 2.82 (s, 3 H, NMe); 2.91 (s, 3 H, NMe); 3.81 (s, 3 H, OMe); 5.58 (d, 1 H, CH, *J* = 7.7 Hz); 5.96 (d, 1 H, CH, *J* = 7.8 Hz); 6.84 (t, 1 H, ArH, *J* = 7.8 Hz); 6.99 (d, 1 H, ArH, *J* = 7.8 Hz); 7.20 (d, 1 H, ArH, *J* = 7.8 Hz); 8.29 (s, 1 H, N=CH); 9.61 (s, 1 H, OH). ^{13}C NMR, δ: 13.0 (SMe); 28.4 (NMe); 30.9 (NMe); 55.9 (OMe); 72.7 (CH); 80.1 (CH); 113.0; 118.6; 119.3; 120.2; 137.0 (N=CH); 145.8; 148.0; 157.8 (C=O); 166.6 (N=C—S). MS (ESI), *m/z*: $[M + H]^+$; found: 350.1276; calculated for $C_{15}H_{19}N_5O_3S$: 350.1281.

(*E*)-1,3-Diethyl-6-[(2-fluorobenzylidene)amino]-5-methylsulfanyl-3,3a,6,6a-tetrahydroimidazo[4,5-*d*]imidazol-2(1*H*)-one

(4d). The yield was 86%, white powder, m.p. 149—151 °C. IR (KBr), ν/cm^{-1}: 1686, 1581, 1566, 1469, 1453, 1399, 1234, 1200, 1187, 1065. ^{1}H NMR, δ: 1.04 (t, 3 H, Me, J = 7.0 Hz); 1.13 (t, 3 H, Me, J = 7.1 Hz); 2.44 (s, 3 H, SMe); 3.12—3.55 (m, 4 H, NCH_2); 5.70 (d, 1 H, CH, J = 7.8 Hz); 6.10 (d, 1 H, CH, J = = 7.9 Hz); 7.27—7.33 (m, 2 H, 3,5-ArH); 7.42—7.49 (m, 1 H, 4-ArH); 7.79 (t, 1 H, 6-ArH, J = 7.5 Hz); 8.04 (s, 1 H, N=CH). ^{13}C NMR, δ: 13.0 (SMe); 13.3 (Me); 13.7 (Me); 36.2 (NCH_2); 37.7 (NCH_2); 70.5 (CH); 78.5 (CH); 116.0 (d, $^2J_{C,F}$ = 20.6 Hz); 121.8 (d, $^2J_{C,F}$ = 10.0 Hz); 124.9 (d, $J_{C,F}$ = 2.9 Hz); 125.8 (d, $J_{C,F}$ = 2.4 Hz); 130.2 (d, $J_{C,F}$ = 4.6 Hz); 131.3 (d, $J_{C,F}$ = = 8.3 Hz); 156.9 (C=O); 160.4 (d, $^1J_{C,F}$ = 249.5 Hz); 166.1 (N=C—S). ^{19}F NMR, δ: −122.47. MS (ESI), m/z: $[M + Na]^+$; found: 372.1262; calculated for $C_{16}H_{20}FN_5OS$: 372.1265.

(*E*)-1,3-Diethyl-6-[(4-methoxybenzylidene)amino]-5-methylsulfanyl-3,3a,6,6a-tetrahydroimidazo[4,5-*d*]imidazol-2(1*H*)-one (4e). The yield was 76%, white powder, m.p. 109—111 °C. IR (KBr), ν/cm^{-1}: 1704, 1605, 1576, 1510, 1467, 1398, 1301, 1249, 1230, 1196, 1187, 1166, 1028. ^{1}H NMR, δ: 1.00 (t, 3 H, Me, J = 6.8 Hz); 1.14 (t, 3 H, Me, J = 7.0 Hz); 2.42 (s, 3 H, SMe); 3.18—3.51 (m, 4 H, NCH_2); 3.80 (s, 3 H, OMe); 5.68 (d, 1 H, CH, J = 7.8 Hz); 5.96 (d, 1 H, CH, J = 7.9 Hz); 7.01 (d, 2 H, ArH, J = 8.4 Hz); 7.61 (d, 2 H, ArH, J = 8.4 Hz); 7.91 (s, 1 H, N=CH). ^{13}C NMR, δ: 12.9 (SMe); 13.3 (Me); 13.9 (Me); 36.2 (NCH_2); 37.6 (NCH_2); 55.3 (OMe); 70.8 (CH); 78.5 (CH); 114.4 (2 C); 127.0; 128.0 (2 C); 137.9 (N=CH); 157.0 (C=O); 160.4; 166.5 (N=C—S). MS (ESI), m/z: $[M + H]^+$; found: 362.1642; calculated for $C_{17}H_{23}N_5O_2S$: 362.1645.

(*E*)-6-[(4-Ethoxy-3-methoxybenzylidene)amino]-1,3-diethyl-5-methylsulfanyl-3,3a,6,6a-tetrahydroimidazo[4,5-*d*]imidazol-2(1*H*)-one (4f). The yield was 75%, white powder, m.p. 138—140 °C. IR (KBr), ν/cm^{-1}: 1692, 1597, 1569, 1514, 1458, 1417, 1384, 1264, 1245, 1230, 1199, 1176, 1133, 1032. ^{1}H NMR, δ: 0.99 (t, 3 H, Me, J = 7.0 Hz); 1.14 (t, 3 H, Me, J = 7.1 Hz); 1.34 (t, 3 H, Me, J = 6.9 Hz); 2.42 (s, 3 H, SMe); 3.19—3.50 (m, 4 H, NCH_2); 3.80 (s, 3 H, OMe); 4.05 (q, 2 H, OCH_2, J = 6.9 Hz); 5.68 (d, 1 H, CH, J = 7.8 Hz); 5.95 (d, 1 H, CH, J = 7.9 Hz); 7.01 (d, 1 H, ArH, J = 8.3 Hz); 7.17 (d, 1 H, ArH, J = 8.3 Hz); 7.27 (s, 1 H, ArH); 7.88 (s, 1 H, N=CH). ^{13}C NMR, δ: 13.0 (SMe); 13.3 (Me); 13.9 (Me); 14.7 (Me); 36.2 (NCH_2); 37.6 (NCH_2); 55.3 (OMe); 63.8 (OCH_2); 70.9 (CH); 78.5 (CH); 108.3; 112.5; 120.7; 127.1; 138.1 (N=CH); 149.1; 149.5; 157.1 (C=O); 166.5 (N=C—S). MS (ESI), m/z: $[M + H]^+$; found: 406.1892; calculated for $C_{19}H_{27}N_5O_3S$: 406.1907.

Synthesis of 4-bromobenzylsulfanyl derivatives 4g—j (general procedure). 4-Bromobenzyl bromide (0.255 mL, 1.02 mmol) was added to a stirred solution of thioglycoluril **1** (1 mmol) and potassium carbonate (0.152 g, 1.1 mmol) in DMSO (5 mL). The resulting mixture was stirred for 5 h, then poured into icy water and kept in a refrigerator for 16 h. The formed precipitate was isolated by filtration, wased with water, dried in air, and recrystallized from methanol.

(*E*)-5-[(4-Bromobenzyl)sulfanyl]-1,3-dimethyl-6-[(2-fluorobenzylidene)amino]-3,3a,6,6a-tetrahydroimidazo[4,5-*d*]imidazol-2(1*H*)-one (4g). The yield was 91%, white powder, m.p. 163—164 °C. IR (KBr), ν/cm^{-1}: 1697, 1584, 1568, 1487, 1459, 1449, 1412, 1398, 1341, 1287, 1242, 1206, 1167, 1040. ^{1}H NMR, δ: 2.85 (s, 3 H, NMe); 2.91 (s, 3 H, NMe); 4.29 (s, 2 H, SCH_2); 5.64 (d, 1 H, CH, J = 7.8 Hz); 6.04 (d, 1 H, CH, J = 7.8 Hz); 7.25—7.30 (m, 2 H, ArH); 7.41—7.46 (m, 3 H, ArH); 7.52 (d, 2 H, ArH, J = 8.3 Hz); 7.76 (t, 1 H, ArH, J = 7.2 Hz); 8.15 (s, 1 H, N=CH). ^{13}C NMR, δ: 28.3 (NMe); 30.8 (NMe); 33.1 (SCH_2); 72.2 (CH); 80.0 (CH); 116.0 (d, $^2J_{C,F}$ = 20.6 Hz); 120.4; 121.8 (d, $^2J_{C,F}$ = 10.0 Hz); 124.9; 126.0; 130.9 (d, $J_{C,F}$ = 4.5 Hz); 131.2 (2 C); 131.3 (d, $J_{C,F}$ = 8.2 Hz); 131.4 (2 C); 137.2 (N=CH); 157.6 (C=O); 160.3 (d, $^1J_{C,F}$ = 249.7 Hz); 165.4 (N=C—S). ^{19}F NMR, δ: −121.58. MS (ESI), m/z: $[M + H]^+$; found: 476.0536; calculated for $C_{20}H_{19}BrFN_5OS$: 476.0550.

(*E*)-5-[(4-Bromobenzyl)sulfanyl]-6-[(3-methoxybenzylidene)amino]-1,3-dimethyl-3,3a,6,6a-tetrahydroimidazo[4,5-*d*]imidazol-2(1*H*)-one (4h). The yield was 84%, white powder, m.p. 178—180 °C. IR (KBr), ν/cm^{-1}: 1715, 1607 (weak), 1568, 1487, 1410, 1264, 1201, 1188, 1044. ^{1}H NMR, δ: 2.84 (s, 3 H, NMe); 2.90 (s, 3 H, NMe); 3.77 (s, 3 H, OMe); 4.27 (s, 2 H, SCH_2); 5.63 (d, 1 H, CH, J = 7.5 Hz); 5.92 (d, 1 H, CH, J = 7.5 Hz); 6.95 (d, 1 H, ArH, J = 7.4 Hz); 7.21—7.26 (m, 2 H, ArH); 7.34 (t, 1 H, ArH, J = 7.6 Hz); 7.41 (d, 2 H, ArH, J = 7.7 Hz); 7.51 (d, 2 H, ArH, J = 7.7 Hz); 8.06 (s, 1 H, N=CH). ^{13}C NMR, δ: 28.3 (NMe); 30.5 (NMe); 33.1 (SCH_2); 55.1 (OMe); 72.1 (CH); 80.0 (CH); 111.6; 115.2; 118.9; 120.3; 129.9; 131.2 (2 C); 131.4 (2 C); 135.8; 137.3; 138.1 (N=CH); 157.5 (C=O); 159.5; 165.6 (N=C—S). MS (ESI), m/z: $[M + H]^+$; found: 488.0744; calculated for $C_{21}H_{22}BrN_5O_2S$: 488.0750.

(*E*)-5-[(4-Bromobenzyl)sulfanyl]-6-[(2-hydroxy-3-methoxybenzylidene)amino]-1,3-dimethyl-3,3a,6,6a-tetrahydroimidazo[4,5-*d*]imidazol-2(1*H*)-one (4i). The yield was 52%, white powder, m.p. 174—176 °C. IR (KBr), ν/cm^{-1}: 1706, 1604 (weak), 1571, 1489, 1453, 1405, 1251, 1206, 1195, 1041. ^{1}H NMR, δ: 2.84 (s, 3 H, NMe); 2.90 (s, 3 H, NMe); 3.80 (s, 3 H, OMe); 4.29 (s, 2 H, SCH_2); 5.61 (d, 1 H, CH, J = 7.7 Hz); 5.96 (d, 1 H, CH, J = 7.7 Hz); 6.81 (t, 1 H, ArH, J = 7.9 Hz); 6.97 (d, 1 H, ArH, J = 7.8 Hz); 7.17 (d, 1 H, ArH, J = 7.8 Hz); 7.41 (d, 2 H, ArH, J = 8.0 Hz); 7.52 (d, 2 H, ArH, J = 8.0 Hz); 8.28 (s, 1 H, N=CH); 9.54 (s, 1 H, OH). ^{13}C NMR, δ: 28.3 (NMe); 30.9 (NMe); 33.1 (SCH_2); 55.9 (OMe); 72.6 (CH); 80.1 (CH); 112.9; 118.3; 119.2; 120.2; 120.4; 131.2 (2 C); 131.4 (2 C); 136.7 (N=CH); 137.2; 145.8; 148.0; 157.6 (C=O); 165.3 (N=C—S). MS (ESI), m/z: $[M + H]^+$; found: 504.0689; calculated for $C_{21}H_{22}BrN_5O_3S$: 504.0699.

(*E*)-6-({2-[(4-Bromobenzyl)oxy]-3-methoxybenzylidene}amino)-5-[(4-bromobenzyl)sulfanyl]-1,3-dimethyl-3,3a,6,6a-tetrahydroimidazo[4,5-*d*]imidazol-2(1*H*)-one (4j). The yield was 23%, white powder, m.p. 166—167 °C. ^{1}H NMR, δ: 2.63 (s, 3 H, NMe); 2.82 (s, 3 H, NMe); 3.86 (s, 3 H, OMe); 4.26 (s, 2 H, SCH_2); 4.97 (d, 1 H, OCH_2, J = 11.2 Hz); 5.03 (d, 1 H, OCH_2, J = 11.2 Hz); 5.59 (d, 1 H, CH, J = 7.5 Hz); 5.76 (d, 1 H, CH, J = 7.5 Hz); 7.10—7.13 (m, 2 H, ArH); 7.28 (t, 1 H, ArH, J = 6.8 Hz); 7.40 (d, 4 H, ArH, J = 7.9 Hz); 7.51 (d, 2 H, ArH, J = 7.9 Hz); 7.59 (d, 2 H, ArH, J = 7.9 Hz); 8.03 (s, 1 H, N=CH). ^{13}C NMR, δ: 28.3 (NMe); 30.7 (NMe); 33.1 (SCH_2); 55.8 (OMe); 72.6 (CH); 73.9 (OCH_2); 80.1 (CH); 113.7; 116.5; 120.3; 121.2; 124.5; 127.7; 130.3 (2 C); 131.2 (2 C); 131.27 (2 C); 131.31 (2 C); 133.3 (N=CH); 136.5; 137.2; 145.9; 152.5; 157.5 (C=O); 165.7 (N=C—S).

The antifungal activity was evaluated *in vitro* according to the known procedure[20,21] using six phytopathogenic fungi species: *Venturia inaequalis*, *Rhizoctonia solani*, *Fusarium oxysporum*, *Fusarium moniliforme*, *Bipolaris sorokiniana*, and *Sclerotinia sclerotiorum*. Triadimefon was used as the reference standard. The effect of the compounds at the concentration of 30 mg L^{-1} on the radial growth of the mycelium was studied. Aliquots of the tested compound solutions in acetone (3 mg mL^{-1}) were

added to the molten sterilized potato-sucrose agar, which was dispensed under aseptic conditions into Petri dishes. The final concentrations of the test substances and acetone in these media were 30 mg L^{-1} and 1%, respectively. Mycelial pieces of the fungi were placed on the solid nutrient medium and incubated at 25 °C for 72 h; then the radial mycelial growth was measured. Each experiment was repeated 3 times. The percentile value of mycelial growth inhibition was calculated acording to Abbott's method.[22]

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