Synthesis, Nematicidal and Antimicrobial Activity of 3-(5-3-Methyl-5-[(3-methyl-7-5-[2-(aryl)-4-oxo-1,3-thiazolan-3-yl]-1,3,4-thiadiazol-2-ylbenzo[*b*]furan-5-yl)methyl]benzo[*b*]furan-7-yl-1,3,4-thiadiazol-2-yl)-2-(aryl)-1,3-thiazolan-4-one

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A new series of 3-(5-3-methyl-5-[(3-methyl-7-5-[2-(aryl)-4-oxo-1,3-thiazolan-3-yl]-1,3,4-thiadiazol-2-ylbenzo-[*b*]furan-5-yl)methyl]benzo[*b*]furan-7-yl-1,3,4-thiadiazol-2-yl)-2-(aryl)-1,3-thiazolan-4-one 5a—j has been synthesized by the reaction of *N*2-[(*E*)-1-(4-methylphenyl)methylidene]-5-(3-methyl-5-[3-methyl-7-(5-[(*E*)-1-(4-methylphenyl)methylidene]amino-1,3,4-thiadiazol-2-yl)benzo[*b*]furan-5-yl]methylbenzo[*b*]furan-7-yl)-1,3,4-thiadiazol-2-amine 4a—j with thioglycolic acid. Chemical structures of all the new compounds were established by their IR, ^{1}H-NMR, ^{13}C-NMR, MS and elemental data. The 5a—j have been assayed for their nematicidal activity against *Ditylenchus myceliophagus* and *Caenorhabditis elegans* by aqueous *in vitro* screening technique. The screened data reveal that, the 5e is most effective against *D. myceliophagus* and *C. elegans* with 50% lethal dose (LD_{50}) of 170 and 190 ppm, respectively and is almost equal to the activity of standard levamisole. The 5h and 5j are also most active against *C. elegans* with LD_{50} of 200 ppm and *D. myceliophagus* with LD_{50} of 190 ppm, respectively. Further, the 5a—j were screened for their antibacterial activity against three representative, Gram-positive bacteria *viz. Bacillus subtilis* ATCC 6633, *Staphylococcus aureus* ATCC 6538p and *Micrococcus luteus* IFC 12708, and three Gram-negative bacteria *viz. Proteus vulgaris* ATCC 3851, *Salmonella typhimurium* ATCC 14028 and *Escherichia coli* ATCC 25922, and also screened for their antifungal activity against four fungal organisms *viz. Candida albicans* ATCC 10231, *Aspergillus fumigatus* HIC 6094, *Trichophyton rubrum* IFO 9185 and *Trichophyton mentagrophytes* IFO 40996. Most of these new compounds showed appreciable activity against the test bacteria and fungi, and emerged as potential molecules for further development.

Key words thiadiazolo-thiazolidine-4-one; nematicidal activity; antimicrobial activity

Several naturally occurring and synthetic benzofuran derivatives are known to be associated with biological and pharmacological activities.[1—6] Among the heterocyclics, thiadiazoles exhibited a broad spectrum of biological effectiveness such as anti-parkinsonism,[7] hypoglycaemic,[8] anticancer,[9] anti-inflammatory,[10] anti-asthmatic[11] and anti-hypertensive[12] activities. Further, there has been considerable interest in the chemistry of thiazolidine-4-one ring system, which is a core structure in various synthetic pharmaceuticals displaying a broad spectrum of biological activities.[13—15] Thiazolidine-4-one ring also occurs in nature; thus actithiazic acid isolated from *Streptomyces* strains exhibits highly specific *in vitro* activity against *Mycobacterium tuberculosis*.[16] Thiazolidine-4-one derivatives are known to exhibit diverse bioactivities such as anti-convulsant,[17] antidiarrheal,[18] antiplatelet activating factor,[19—21] anti-histaminic,[22,23] antimicrobial,[24,25] anti-diabetic,[26] cyclooxygenase (COX) inhibitory,[27] Ca^{2+}-channel blocker,[28] platelet activating factor (PAF) antagonist,[29] cardioprotective,[30] anti-ischemic,[31] anticancer,[32] tumour necrosis factor-α antagonist[33] and nematicidal activities.[34]

Nematodes are tiny worms, some of them are plant parasites and can play an important role in the predisposition of the host plant to the invasion by secondary pathogens.[35] Plants attacked by nematodes show retarded growth and development, as well as loss in the quality and quantity of the harvest. The nematicide use is slated for reduction due to environmental problems, and human and animal health concerns. For example, effective nematicides such as dibromochloropropane (DBCP) and ethylenedibromide (EDB) have been withdrawn from the market due to their deleterious effects on humans and the environment. Methyl bromide, the most effective and widely used fumigant for soil borne pests including nematodes, has already been banned. The use of nonfumigant nematicides, based on organophosphates and carbamates, is expected to increase the withdrawal of methyl bromide, which will bring about new environmental concerns. In fact, the highly toxic aldicarb used to control insects and nematodes has been detected in ground water.[36] Therefore, alternative nematode control methods or less toxic nematicides need to be developed.[37] One way of searching for such nematicidal compounds is to screen naturally occurring compounds in plants. Several such compounds, *e.g.* alkaloids, phenols, sesquiterpenes, diterpenes, polyacetylenes and thienyl derivatives have nematicidal activity.[38] For example, α-terthienyl is a highly effective nematicidal compound.[39] Other compounds with nematicidal activity have been isolated from plants, mainly from the family *Asteraceae*.[38] However, compounds of plant origin and their analogs have not been developed into commercial nematicides, hence there is a need to develop commercial synthesis.

In recent years, attention has been increasingly paid to the synthesis of bis-heterocyclic compounds which exhibit various biological activities[40—43] including antibacterial, fungicidal, tuberculostatic and plant growth regulative properties. Furthermore, it was indicated that bis-heterocyclic compounds displayed much better antibacterial activity than the mono heterocyclic compounds.[44—47]

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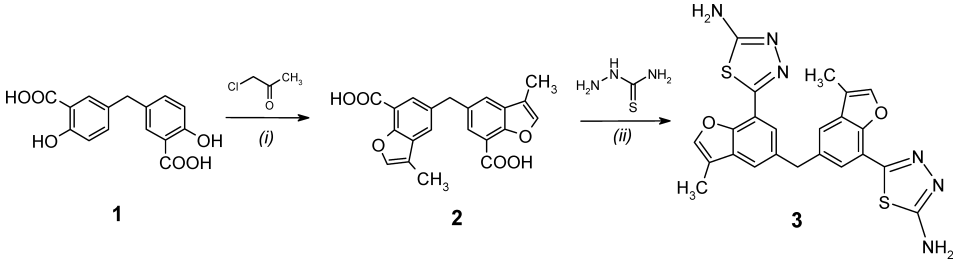
Inspired by the biological profile of benzofuran, thiadiazole, thiazolidine-4-one and their increasing importance in pharmaceutical and biological field, and in continuation of our research on biologically active heterocycles,[48—51] and in order to enhance the biological activity, it was thought of interest to accommodate thiadiazole and thiazolidine-4-one moieties in a single molecular frame work and to synthesize the bis-heterocyclics for enhancing biological activity. The present investigation deals with the use of bis-salicylic acid in the synthesis of some interesting bis-thiadiazolo-thiazolidin-4-ones of expected pharmacological action and to study their effect on nematodes, bacteria and fungi.

Results and Discussion

Synthesis Compound **1** was prepared according to the procedure described in the literature.[52] Condensation of **1** with chloroacetone in the presence of K_2CO_3 and catalytic amount of KI at reflux for 12 h followed by cyclization in alc. KOH at reflux for 18 h gave 5-[(7-carboxy-3-methylbenzo-[*b*]furan-5-yl)methyl]-3-methylbenzo[*b*]furan-7-carboxylic acid **2** in 72% yield. Further, condensation of **2** with thiosemicarbazide in ethanol at reflux for 10 h, followed by cyclization in conc. H_2SO_4 at room temperature afforded 5-(5-{[7-(5-amino-1,3,4-thiadiazol-2-yl)-3-methylbenzo[*b*]-furan-5-yl]methyl}-3-methylbenzo[*b*]furan-7-yl)-1,3,4-thiadiazol-2-amine **3** in 78% yield (Chart 1).

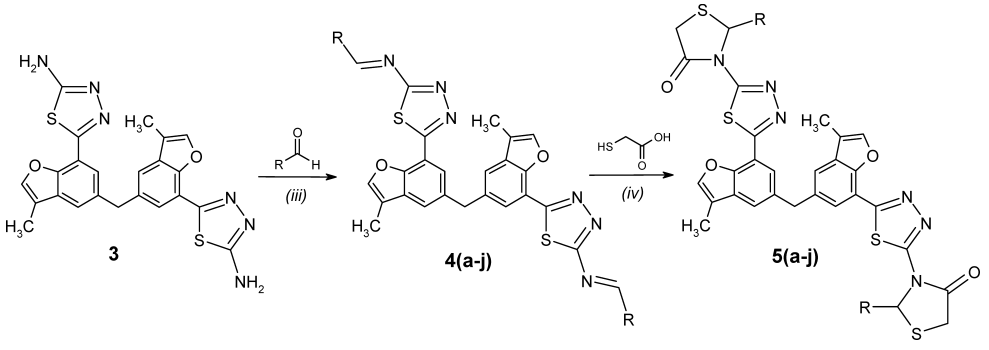
Compound **3** on reaction with the corresponding arylaldehyde in the presence of acetic acid at reflux for 3 h furnished the corresponding *N*2-[(*E*)-1-(aryl))methylidene]-5-(3-methyl-5-[3-methyl-7-(5-[(*E*)-1-(aryl)methylidene]amino-1,3,4-thiadiazol-2-yl)benzo[*b*]furan-5-yl]methylbenzo[*b*]-furan-7-yl)-1,3,4-thiadiazol-2-amine **4a**—**j** in 74—79% yield. The **4a**—**j** when reacted with thioglycolic acid in the presence of $ZnCl_2$ in *N*,*N*-dimethylformamide (DMF) at reflux temperature for 6 h afforded 3-(5-3-methyl-5-[(3-methyl-7-5-[2-(aryl)-4-oxo-1,3-thiazolan-3-yl]-1,3,4-thiadiazol-2-yl-benzo[*b*]furan-5-yl)methyl]benzo[*b*]furan-7-yl-1,3,4-thiadiazol-2-yl)-2-(aryl)-1,3-thiazolan-4-one **5a**—**j** in 71—82% yield (Chart 2). The versatility of the reaction is well demonstrated by the fact that a variety of arylaldehydes, with electron-releasing and electron-withdrawing groups, afforded their corresponding **5a**—**j** in good yields. The structures of newly described compounds were confirmed by elemental analysis, IR, ^{1}H-NMR, ^{13}C-NMR and MS spectral data.

In the IR spectra of **5a**—**j** appearance of amide carbonyl (C=O) absorption band at about 1698 cm^{-1}, and the band 712 cm^{-1} corresponding to the C–S–C stretching vibration provided the evidence for ring closure. Further support was obtained from the ^{1}H-NMR spectra, the N–CH–S proton and CH_2–S protons of thiazolidine-4-one ring appeared at 5.94 and 3.67 ppm, respectively as singlets. These signals demonstrate that the cyclization has occurred. In the ^{13}C-NMR



Reagents and conditions: (i) Acetone, K_2CO_3, KI, reflux 12 h, alc. KOH, reflux 18 h, 72%; (ii) EtOH, reflux 10 h, Conc. H_2SO_4, rt, 78%.

Chart 1



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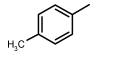
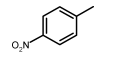
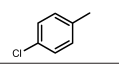
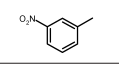
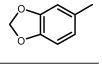
a		c		e		g		i	
b		d		f		h		j	

Reagents and conditions: (iii) AcOH, reflux 3 h, 74—79%; (iv) DMF, $ZnCl_2$, reflux 6 h, 71—82%.

Chart 2

spectra, the prominent signals corresponding to the carbons of thiadiazole and thiazolidine-4-one ring in all the compounds observed nearly at 173.2 and 154.9 ppm and at 170.5, 72.0 and 33.9 ppm, respectively, are proof of further evidence of their structures. In summary all the synthesized compounds exhibited satisfactory spectral data consistent with their molecular structures.

Biological Properties. Nematicidal Activity All the newly synthesized compounds **5a**—**j** in this study were assayed for their nematicidal activity against *Ditylenchus myceliophagus* and *Caenorhabditis elegans* by aqueous *in vitro* screening technique[53] at various concentrations. The nematicidal activity of each test compound was compared with the standard drug levamisole. The results have been expressed in terms of 50% lethal dose (LD_{50}) *i.e.* median lethal dose at which 50% nematodes became immobile (dead). The screened data reveal that, **5e** is the most effective against *D. myceliophagus* and *C. elegans* with LD_{50} of 170 and 190 ppm, respectively. The compounds **5h** and **5j** are also most active against *C. elegans* with LD_{50} of 200 ppm and *D. myceliophagus* with LD_{50} of 190 ppm, respectively. The activity of **5e** is almost equal to the activity of standard levamisole, the other test compounds showed moderate activity. The LD_{50} values of the compounds screened are presented in Table 1.

Antibacterial Activity Compounds **5a**—**j** were assayed for their antibacterial activity against three representative Gram-positive bacteria *viz. Bacillus subtilis* ATCC 6633, *Staphylococcus aureus* ATCC 6538p and *Micrococcus luteus* IFC 12708, and three Gram-negative bacteria *viz. Proteus vulgaris* ATCC 3851, *Salmonella typhimurium* ATCC 14028 and *Escherichia coli* ATCC 25922 by the broth dilution method, recommended by National Committee for Clinical Laboratory Stadards (NCCLS).[54] The lowest concentration (highest dilution) required to arrest the growth of bacteria was regarded as minimum inhibitory concentration (MIC, μg/ml), was determined for all the compounds and compared with the control. The MIC values of the compounds assayed are presented in Table 2. All assays included the solvent and reference controls, Ampicillin was used as standard drug.

The investigation of antibacterial screening data revealed that all the tested compounds exhibited interesting biological activity, however, with a degree of variation. Compound **5c** is highly active against all the microorganisms employed, except *Escherichia coli*, at 1.56 μg/ml concentration; it is almost equal to the standard. Compound **5j** is also highly active but only against *M. luteus* and *P. vulgaris* at the same concentration as **5c**. Compound **5e** also showed good antibacterial activity against *B. subtilis*, *S. aureus*, *M. Luteus* and *S. typhimurium*. Compound **5a** is almost inactive towards *M. luteus*, *P. vulgaris* and *E. coli*. The remaining compounds showed moderate good activity.

Antifungal Activity Compounds **5a**—**j** were also screened for their antifungal activity against four fungal organisms *viz. Candida albicans* ATCC 10231, *Aspergillus fumigatus* HIC 6094, *Trichophyton rubrum* IFO 9185, and *Trichophyton mentagrophytes* IFO 40996 in dimethyl sulfoxide (DMSO) by broth dilution method.[55] Amphotericin B was used as a standard drug and the minimum inhibitory concentration (MIC, μg/ml) were measured and compared with controls, the MIC values of the compounds screened are given in Table 3.

The antifungal screening data showed good activity of the test compounds. Among the screened compounds, **5c** is highly active against *T. rubrum*, *T. mentagrophytes*, **5e** is also active against only *C. albicans* and **5i** is highly active against *C. albicans*, *T. mentagrophytes*, the activity of these compounds are almost equal to the standard. It is interesting to note that **5e** and **5i** showed good antifungal activity towards *C. albicans* at the concentration of 3.12 μg/ml, which is less than the concentration of the standard.

Table 1. Median Lethal Dose LD_{50} (ppm) of Compounds **5a**—**j** against Tested Nematodes

Compound	**5a**	**5b**	**5c**	**5d**	**5e**	**5f**	**5g**	**5h**	**5i**	**5j**	Levamisole
D. myceliophagus	790	850	560	600	170	270	950	430	570	190	170
C. elegans	760	770	360	550	190	220	870	200	610	780	180

LD_{50}, median lethal dose (the concentration at which 50% nematodes became immobile).

Table 2. Antibacterial Activity of Compounds **5a**—**j**

Compound	Minimum inhibitory concentration (MIC) in μg/ml					
	B. subtilis	*S. aureus*	*M. luteus*	*P. vulgaris*	*S. typhimurium*	*E. coli*
5a	25.0	25.0	>50.0	>50.0	25.0	>50.0
5b	12.5	12.5	12.5	12.5	12.5	25.0
5c	1.56	1.56	1.56	1.56	1.56	12.5
5d	12.5	12.5	6.25	>50.0	12.5	25.0
5e	6.25	6.25	1.56	1.56	3.12	1.56
5f	25.0	12.5	3.12	12.5	6.25	25.0
5g	25.0	25.0	50.0	12.5	50.0	>50.0
5h	6.25	12.5	12.5	25.0	12.5	25.0
5i	3.12	6.25	12.5	6.25	12.5	12.5
5j	12.5	12.5	1.56	1.56	12.5	25.0
Ampicillin	1.56	1.56	1.56	3.12	3.12	12.5

MIC, minimum inhibitory concentration (the lowest concentration that inhibited the bacterial growth). Standard deviation 0.05.

Table 3. Antifungal Activity of Compounds **5a**—**j**

Compound	Minimum inhibitory concentration (MIC) in μg/ml			
	C. albicans	*A. fumigatus*	*T. rubrum*	*T. mentagropytes*
5a	25.0	12.5	>50.0	25.0
5b	25.0	25.0	25.0	25.0
5c	12.5	6.25	3.12	3.12
5d	25.0	12.5	6.25	12.5
5e	3.12	12.5	12.5	25.0
5f	50.0	25.0	12.5	12.5
5g	25.0	25.0	12.5	25.0
5h	6.25	12.5	25.0	12.5
5i	3.12	6.25	6.25	3.12
5j	50.0	50.0	50.0	25.0
Amphotericin B	6.25	3.12	3.12	3.12

MIC, minimum inhibitory concentration (the lowest concentration that inhibited the fungal growth). Standard deviation 0.05.

Conclusion

In conclusion, a new series of 3-(5-3-methyl-5-[(3-methyl-7-5-[2-(aryl)-4-oxo-1,3-thiazolan-3-yl]-1,3,4-thiadiazol-2-yl-benzo[*b*]furan-5-yl)methyl]benzo[*b*]furan-7-yl-1,3,4-thiadiazol-2-yl)-2-(aryl)-1,3-thiazolane-4-one **5a**—**j** has been synthesized and evaluated for their nematicidal activity, most of the compounds showed appreciable nematicidal activity. The antibacterial (MIC) activity and antifungal (MIC) activity of these compounds were also evaluated against various bacteria and fungi. Many of the synthesized compounds showed good activity against the test bacteria and fungi and emerged as potential molecules for further development.

Experimental

General Reagents were of commercial grade and were used as supplied or were prepared according to procedures described in literature. Solvents except analytical reagent grade were dried and purified according to literature when necessary. Reactions were monitored by thin-layer chromatography (TLC) on pre-coated silica gel F_{254} plates from Merck and compounds visualized either by exposure to UV light or dipping in 1% aqueous potassium permanganate solution. Chromatographic columns 70—230 mesh silica gel for separations were used. Melting points were determined through a Fisher–Johns apparatus and are uncorrected. IR spectra were recorded using KBr disk on a Perkin–Elmer FT-IR spectrometer. The ^{1}H- and ^{13}C-NMR spectra were recorded on a Varian Gemini spectrometer (300 MHz for ^{1}H- and 75 MHz for ^{13}C-NMR). Chemical shifts are reported in δ ppm units with respect to tetramethylsilane (TMS) as internal standard and coupling constants (J) are reported in Hz units. Mass spectra were recorded on a VG micro mass 7070H spectrometer. Elemental analyses (C, H, N) determined by means of a Perkin-Elmer 240 CHN elemental analyzer, were within $\pm$0.4% of theory.

Typical Procedure 5-[(7-Carboxy-3-methylbenzo[*b*]furan-5-yl)-methyl]-3-methylbenzo[*b*]furan-7-carboxylic Acid (2) To a stirred solution of **1** (5 mmol), anhydrous potassium carbonate (3 mmol) and a catalytic amount of potassium iodide in dry acetone (30 ml), was added drop wise a solution of chloroacetone (10 mmol) in dry acetone (20 ml) at reflux temperature. Reflux was continued for 12 h. The reaction mixture was concentrated to dryness and then transferred to ice water, and the solid separated was collected by filtration. The crude product was dissolved in ethanolic potassium hydroxide (10%, 100 ml) and further refluxed for 18 h. The excess ethanol was then removed by distillation *in vacuo*, the reaction mixture was poured into ice-cold aq. HCl and the solid collected by filtration, purified by column chromatography using pet-ether (60—80 °C) as eluent to give pure **2** as yellow solid. Yield 72%, mp 182—184 °C. IR (KBr) cm^{-1}: 3300—3200, 3037, 1695, 1030. ^{1}H-NMR (DMSO-d_6) δ: 9.90 (s, 2H, OH), 7.79 (s, 2H, Ar-H), 7.65—7.60 (m, 4H, Ar-H), 4.11 (s, 2H, CH_2), 2.39 (s, 6H, CH_3). ^{13}C-NMR (DMSO-d_6) δ: 172.6, 152.7, 143.9, 135.2, 132.9, 132.0, 124.6, 121.2, 119.1, 42.7, 9.2. MS *m*/*z*: 365 (M^++1, 10%), 106 (100%). *Anal.* Calcd for $C_{21}H_{16}O_8$: C, 69.23; H, 4.43. Found: C, 69.18; H, 4.40.

Typical Procedure 5-(5-{[7-(5-Amino-1,3,4-thiadiazol-2-yl)-3-methylbenzo[*b*]furan-5-yl]methyl}-3-methylbenzo[*b*]furan-7-yl)-1,3,4-thiadiazol-2-amine (3) A mixture of **2** (5 mmol) and thiosemicarbazide (10 mmol) in acetone (20 ml) was refluxed for 10 h. The reaction mixture was allowed to cool, and the solid separated was collected by filtration. The crude product was dissolved in conc. H_2SO_4 (5 ml) and stirred at room temperature for few minutes and left overnight. It was then poured on crussed ice, the resulting suspension was kept in ammonical water (25 ml) for 4 h, filtered the solid and recrystallized from ethanol to give pure **3** as yellow solid. Yield 78%, mp 192—194 °C. IR (KBr) cm^{-1}: 3350, 3050, 2985, 1605, 1030, 712. ^{1}H-NMR (DMSO-d_6) δ: 7.65—7.60 (m, 4H, Ar-H), 7.47 (s, 2H, Ar-H), 4.92 (s, 4H, NH_2), 4.10 (s, 2H, CH_2). ^{13}C-NMR (DMSO-d_6) δ: 168.2, 163.4, 153.4, 141.7, 136.1, 130.6, 128.2, 127.1, 123.4, 119.1, 42.6, 9.1. MS *m*/*z*: 475 (M^++1, 18%), 106 (100%). *Anal.* Calcd for $C_{23}H_{18}N_6O_2S_2$: C, 58.21; H, 3.82; N, 17.71. Found: C, 58.16; H, 3.80; N, 17.69.

Typical Procedure *N*2-[(*E*)-1-(4-methylphenyl)methylidene]-5-(3-methyl-5-[3-methyl-7-(5-[(*E*)-1-(4-methylphenyl)methylidene]amino-1,3,4-thiadiazol-2-yl)benzo[*b*]furan-5-yl]methylbenzo[*b*]furan-7-yl)-1,3,4-thiadiazol-2-amine (4a) A mixture of **3** (5 mmol), *p*-methylbenzaldehyde (10 mmol) and acetic acid (0.5 ml) was refluxed in toluene for 3 h using a Dean-stark apparatus and the water formed was removed azeiotropically. The progress of the reaction was checked by TLC using toluene : ethyl acetate (4 : 1) as an eluent. After completion of the reaction, solvent was removed by distillation to give solid, which was filtered, and recrystallized from ethyl alcohol to give pure **4a** as yellow solid. Yield 74%, mp 186—188 °C. IR (KBr) cm^{-1}: 3052, 2988, 1625, 1610, 1070, 714. ^{1}H-NMR (DMSO-d_6) δ: 8.76 (s, 2H, CH), 7.70 (d, J=7.6 Hz, 4H, Ar-H), 7.59 (s, 2H, Ar-H), 7.55—7.50 (m, 4H, Ar-H), 7.00 (d, J=7.6 Hz, 4H, Ar-H), 4.12 (s, 2H, CH_2), 2.44 (s, 6H, CH_3), 2.21 (s, 6H, CH_3). ^{13}C-NMR (DMSO-d_6) δ: 165.3, 162.7, 161.4, 150.6, 143.4, 135.6, 135.0, 133.9, 131.7, 129.6, 128.7, 126.4, 122.8, 118.5, 42.0, 20.7, 9.7. MS *m*/*z*: 678 (M^+). *Anal.* Calcd for $C_{39}H_{30}N_6O_2S_2$: C, 69.01; H, 4.45; N, 12.38. Found: C, 68.95; H, 4.40; N, 12.33. The other compounds (**4b**—**j**) were prepared using the same procedure.

Typical Procedure 3-(5-3-Methyl-5-[(3-methyl-7-5-[2-(aryl)-4-oxo-1,3-thiazolan-3-yl]-1,3,4-thiadiazol-2-ylbenzo[*b*]furan-5-yl)methyl]benzo-[*b*]furan-7-yl-1,3,4-thiadiazol-2-yl)-2-(aryl)-1,3-thiazolan-4-one (5a—j) A mixture of **4** (5 mmol), thioglycolic acid (12 mmol) in *N*,*N*-dimethylformamide (40 ml) with a pinch of anhydrous $ZnCl_2$, was refluxed for 6 h, the progress of the reaction was checked by TLC using toluene : ether (3 : 1) as an eluent. The reaction mixture was cooled to room temperature and then poured into crussed ice. It was set-aside at room temperature overnight. The solid thus separated was filtered, washed several times with water and purified by column chromatography on silica-gel with hexane–ethyl acetate as eluent to afford pure compounds.

3-(5-3-Methyl-5-[(3-methyl-7-5-[2-(4-methylphenyl)-4-oxo-1,3-thiazolan-3-yl]-1,3,4-thiadiazol-2-ylbenzo[*b*]furan-5-yl)methyl]benzo[*b*]-furan-7-yl-1,3,4-thiadiazol-2-yl)-2-(4-methylphenyl)-1,3-thiazolan-4-one (5a) This was obtained by reacting **4a** (3.38 g) and thioglycolic acid (1.12 g) as described in the typical procedure and isolated as brown solid. Yield 71%, mp 210—212 °C. IR (KBr) cm^{-1}: 3062, 1698, 1612, 1604, 1475, 1066, 712. ^{1}H-NMR (DMSO-d_6) δ: 7.64 (s, 2H, Ar-H), 7.49 (s, 2H, Ar-H), 7.25—7.19 (m, 6H, Ar-H), 7.10 (d, J=7.9 Hz, 4H, Ar-H), 5.94 (s, 2H, CH), 4.20 (s, 2H, CH_2), 3.67 (s, 4H, CH_2), 2.36 (s, 6H, CH_3), 2.24 (s, 6H, CH_3). ^{13}C-NMR (DMSO-d_6) δ: 173.2, 170.6, 154.9, 150.8, 142.9, 137.9, 135.2, 135.0, 132.0, 127.4, 126.9, 125.8, 124.6, 123.7, 118.9, 72.0, 42.0, 33.9, 22.1, 9.20. MS *m*/*z*: 828 (M^+). *Anal.* Calcd for $C_{43}H_{34}N_4O_4S_4$: C, 62.45; H, 4.14; N, 10.16. Found: C, 62.90; H, 4.10; N, 10.11.

2-(4-Chlorophenyl)-3-(5-5-[(7-5-[2-(4-chlorophenyl)-4-oxo-1,3-thiazolan-3-yl]-1,3,4-thiadiazol-2-yl-3-methylbenzo[*b*]furan-5-yl)methyl]-3-methylbenzo[*b*]furan-7-yl-1,3,4-thiadiazol-2-yl)-1,3-thiazolan-4-one (5b) This was obtained by reacting **4b** (3.6 g) and thioglycolic acid (1.12 g) as described in the typical procedure and isolated as brown solid. Yield 73%, mp 201—203 °C. IR (KBr) cm^{-1}: 3062, 1696, 1612, 1604, 1475, 1065, 712, 685. ^{1}H-NMR (DMSO-d_6) δ: 7.64 (s, 2H, Ar-H), 7.49 (s, 2H, Ar-H), 7.30 (d, J=8.2 Hz, 4H, Ar-H), 7.25—7.19 (m, 6H, Ar-H), 5.94 (s, 2H, CH), 4.20 (s, 2H, CH_2), 3.67 (s, 4H, CH_2), 2.36 (s, 6H, CH_3). ^{13}C-NMR (DMSO-d_6) δ: 173.2, 170.5, 154.9, 150.8, 142.7, 138.9, 135.2, 133.1, 132.0, 129.7, 128.6, 127.4, 126.8, 125.8, 123.7, 118.9, 72.0, 42.0, 33.9, 9.20. MS *m*/*z*: 868 (M^+). *Anal.* Calcd for $C_{41}H_{28}Cl_2N_6O_4S_4$: C, 56.74; H, 3.25; N, 9.68. Found: C, 56.70; H, 3.21; N, 9.70.

3-(5-3-Methyl-5-[(3-methyl-7-5-[2-(4-nitrophenyl)-4-oxo-1,3-thiazolan-3-yl]-1,3,4-thiadiazol-2-ylbenzo[*b*]furan-5-yl)methyl]benzo[*b*]-furan-7-yl-1,3,4-thiadiazol-2-yl)-2-(4-nitrophenyl)-1,3-thiazolan-4-one (5c) This was obtained by reacting **4c** (3.7 g) and thioglycolic acid (1.12 g)

as described in the typical procedure and isolated as yellow solid. Yield 74%, mp 198—200 °C. IR (KBr) cm^{-1}:3065, 1698, 1612, 1604, 1520, 1475, 1370, 1066, 712. ^{1}H-NMR (DMSO-d_6) δ: 7.69 (d, J=8.2 Hz, 4H, Ar-H), 7.60 (s, 2H, Ar-H), 7.49 (s, 2H, Ar-H), 7.41 (d, J=8.2 Hz, 4H, Ar-H), 7.24 (s, 2H, Ar-H), 5.94 (s, 2H, CH), 4.20 (s, 2H, CH_2), 3.67 (s, 4H, CH_2), 2.36 (s, 6H, CH_3). ^{13}C-NMR (DMSO-d_6) δ: 173.3, 170.5, 154.8, 150.7, 142.8, 146.2, 146.0, 135.2, 132.0, 128.1, 127.4, 126.8, 125.8, 123.8, 123.0, 118.8, 72.0, 42.0, 34.0, 9.20. MS m/z: 888 (M^+). *Anal.* Calcd for $C_{41}H_{28}N_8O_8S_4$: C, 55.40; H, 3.17; N, 12.61. Found: C, 55.36; H,3.10; N,12.55.

3-(5-3-Methyl-5-[(3-methyl-7-5-[2-(3-nitrophenyl)-4-oxo-1,3-thiazolan-3-yl]-1,3,4-thiadiazol-2-ylbenzo[*b*]furan-5-yl)methyl]benzo[*b*]-furan-7-yl-1,3,4-thiadiazol-2-yl)-2-(3-nitrophenyl)-1,3-thiazolan-4-one (5d) This was obtained by reacting **4d** (3.7 g) and thioglycolic acid (1.12 g) as described in the typical procedure and isolated as brown solid. Yield 76%, mp 209—211 °C. IR (KBr) cm^{-1}: 3070, 1696, 1612, 1604, 1520, 1475, 1370, 1066, 712. ^{1}H-NMR (DMSO-d_6) δ: 8.20 (s, 2H, CH), 8.11 (d, J=8.4 Hz, 2H, Ar-H), 7.64 (s, 2H, Ar-H), 7.56 (d, J=7.8 Hz, 4H, Ar-H), 7.49 (s, 2H, Ar-H), 7.41 (d, J=7.8 Hz, 4H, Ar-H), 7.24 (s, 2H, Ar-H), 6.11 (s, 2H, CH), 4.20 (s, 2H, CH_2), 3.67 (s, 4H, CH_2), 2.36 (s, 6H, CH_3). ^{13}C-NMR (DMSO-d_6) δ: 173.5, 170.6, 154.7, 150.6, 142.7, 141.4, 147.6, 135.2, 132.8, 132.0, 130.1, 127.3, 126.7, 125.8, 124.5, 123.7, 120.5, 118.6, 72.58, 42.0, 34.0, 9.20. MS m/z: 888 (M^+). *Anal.* Calcd for $C_{41}H_{28}N_8O_8S_4$: C, 55.40; H, 3.17; N,12.61. Found: C, 55.37; H, 3.14; N, 12.65.

2-(4-Hydroxyphenyl)-3-(5-5-[(7-5-[2-(4-hydroxyphenyl)-4-oxo-1,3-thiazolan-3-yl]-1,3,4-thiadiazol-2-yl-3-methylbenzo[*b*]furan-5-yl)methyl]-3-methylbenzo[*b*]furan-7-yl-1,3,4-thiadiazol-2-yl)-1,3-thiazolan-4-one (5e) This was obtained by reacting **4e** (3.41 g) and thioglycolic acid (1.12 g) as described in the typical procedure and isolated as brown solid. Yield 77%, mp 188—190 °C. IR (KBr) cm^{-1}: 3372, 3047, 1699, 1612, 1604, 1475, 1064, 712. ^{1}H-NMR (DMSO-d_6) δ: 7.64 (s, 2H, Ar-H), 7.49 (s, 2H, Ar-H), 7.25—7.19 (m, 6H, Ar-H), 6.99 (d, J=8.2 Hz, 4H, Ar-H), 5.94 (s, 2H, CH), 5.00 (s, 2H, OH), 4.20 (s, 2H, CH_2), 3.67 (s, 4H, CH_2), 2.36 (s, 6H, CH_3). ^{13}C-NMR (DMSO-d_6) δ: 173.2, 170.5, 157.9, 154.6, 150.6, 142.8, 134.9, 135.2, 132.0, 127.3, 126.8, 126.0, 125.8, 123.6, 118.5, 114.7, 72.0, 42.0, 34.0, 9.20. MS m/z: 830 (M^+). *Anal.* Calcd for $C_{41}H_{30}N_6O_6S_4$: C, 59.26; H, 3.64; N,10.11. Found: C, 59.29; H, 3.60; N, 10.07.

2-(2-Hydroxyphenyl)-3-(5-5-[(7-5-[2-(2-hydroxyphenyl)-4-oxo-1,3-thiazolan-3-yl]-1,3,4-thiadiazol-2-yl-3-methylbenzo[*b*]furan-5-yl)methyl]-3-methylbenzo[*b*]furan-7-yl-1,3,4-thiadiazol-2-yl)-1,3-thiazolan-4-one (5f) This was obtained by reacting **4f** (3.41 g) and thioglycolic acid (1.12 g) as described in the typical procedure and isolated as brown solid. Yield 75%, mp 190—192 °C. IR (KBr) cm^{-1}: 3272, 3049, 1698, 1612, 1604, 1475, 1062, 710. ^{1}H-NMR (DMSO-d_6) δ: 7.64 (s, 2H, Ar-H), 7.49 (s, 2H, Ar-H), 7.25—7.19 (m, 6H, Ar-H), 6.88—6.78 (m, 4H, Ar-H), 6.61 (s, 2H, OH), 6.11 (s, 2H, CH), 4.20 (s, 2H, CH_2), 3.67 (s, 4H, CH_2), 2.36 (s, 6H, CH_3). ^{13}C-NMR (DMSO-d_6) δ: 173.2, 170.4, 154.8, 152.7, 150.8, 142.7, 135.2, 132.0, 128.4, 127.3, 127.0, 126.7, 125.8, 123.5, 122.6, 120.6, 118.6, 115.7, 66.7, 42.0, 34.1, 9.30. MS m/z: 830 (M^+). *Anal.* Calcd for $C_{41}H_{30}N_6O_6S_4$: C, 59.26; H, 3.64; N, 10.11. Found: C, 59.20; H, 3.59; N, 10.09.

2-[4-(Dimethylamino)phenyl]-3-[5-(5-[7-(5-2-[4-(dimethylamino)-phenyl]-4-oxo-1,3-thiazolan-3-yl-1,3,4-thiadiazol-2-yl)-3-methylbenzo-[*b*]furan-5-yl]methyl-3-methylbenzo[*b*]furan-7-yl)-1,3,4-thiadiazol-2-yl]-1,3-thiazolan-4-one (5g) This was obtained by reacting **4g** (3.68 g) and thioglycolic acid (1.12 g) as described in the typical procedure and isolated as black solid. Yield 74%, mp 222—224 °C. IR (KBr) cm^{-1}: 3062, 1698, 1612, 1605, 1475, 1065, 711. ^{1}H-NMR (DMSO-d_6) δ: 7.64 (s, 2H, Ar-H), 7.49 (s, 2H, Ar-H), 7.24 (s, 2H, Ar-H), 7.14 (d, J=7.8 Hz, 4H, Ar-H), 6.38 (d, J=7.8 Hz, 4H, Ar-H), 5.94 (s, 2H, CH), 4.20 (s, 2H, CH_2), 3.67 (s, 4H, CH_2), 3.00 (s, 12H, CH_3), 2.36 (s, 6H, CH_3). ^{13}C-NMR (DMSO-d_6) δ: 173.1, 170.3, 154.7, 150.6, 142.9, 142.6, 135.2, 134.6, 132.0, 127.9, 127.0, 126.8, 125.7, 123.6, 118.7, 112.4, 72.0, 44.5, 42.0, 34.0, 9.20. MS m/z: 886 (M^+). *Anal.* Calcd for $C_{45}H_{40}N_8O_4S_4$: C, 61.07; H, 4.55; N, 12.66. Found: C, 61.00; H, 4.50; N, 12.60.

2-(4-Hydroxy-3-methoxyphenyl)-3-(5-5-[(7-5-[2-(4-hydroxy-3-methoxyphenyl)-4-oxo-1,3-thiazolan-3-yl]-1,3,4-thiadiazol-2-yl-3-methylbenzo[*b*]furan-5-yl)methyl]-3-methylbenzo[*b*]furan-7-yl-1,3,4-thiadiazol-2-yl)-1,3-thiazolan-4-one (5h) This was obtained by reacting **4h** (3.71 g) and thioglycolic acid (1.12 g) as described in the typical procedure and isolated as black solid. Yield 79%, mp 237—239 °C. IR (KBr) cm^{-1}: 3290, 3061, 1697, 1612, 1604, 1475, 1066, 1030, 712. ^{1}H-NMR (DMSO-d_6) δ: 7.64 (s, 2H, Ar-H), 7.49 (s, 2H, Ar-H), 7.24 (s, 2H, Ar-H), 7.14—6.90 (m, 6H, Ar-H), 5.94 (s, 2H, CH), 4.87 (s, 2H, OH), 4.20 (s, 2H, CH_2), 3.77 (s, 6H, CH_3), 3.67 (s, 4H, CH_2), 2.36 (s, 6H, CH_3). ^{13}C-NMR (DMSO-d_6) δ: 173.2, 170.4, 154.8, 150.8, 148.7, 147.8, 142.9, 135.9, 135.1, 132.1, 127.3, 126.7, 125.8, 123.6, 119.3, 118.8, 109.6, 56.0, 42.0, 34.0, 9.31. MS m/z: 892 (M^+). *Anal.* Calcd for $C_{43}H_{34}N_6O_8S_4$: C, 57.96; H, 3.85; N, 9.43. Found: C, 57.90; H, 3.81; N, 9.38.

2-(2-Furyl)-3-(5-5-[(7-5-[2-(2-furyl)-4-oxo-1,3-thiazolan-3-yl]-1,3,4-thiadiazol-2-yl-3-methylbennzo[*b*]furan-5-yl)methyl]-3-methylbenzo-[*b*]furan-7-yl-1,3,4-thiadiazol-2-yl)-1,3-thiazolan-4-one (5i) This was obtained by reacting **4i** (3.15 g) and thioglycolic acid (1.12 g) as described in the typical procedure and isolated as black solid. Yield 82%, mp 177—179 °C. IR (KBr) cm^{-1}: 3070, 1698, 1610, 1604, 1475, 1062, 714. ^{1}H-NMR (DMSO-d_6) δ: 7.64 (s, 2H, Ar-H), 7.49 (s, 2H, Ar-H), 7.56 (d, J=8.0 Hz, 2H, Ar-H), 7.24 (s, 2H, Ar-H), 6.50—6.40 (m, 4H, Ar-H), 6.22 (s, 2H, CH), 4.20 (s, 2H, CH_2), 3.67 (s, 4H, CH_2), 2.36 (s, 6H, CH_3). ^{13}C-NMR (DMSO-d_6) δ: 173.0, 170.1, 154.7, 150.8, 142.9, 147.6, 145.8, 144.3, 135.2, 132.1, 127.2, 126.8, 125.9, 123.6, 121.7, 118.9, 106.1, 58.7, 42.0, 34.2, 9.21. MS m/z: 778 (M^+). *Anal.* Calcd for $C_{37}H_{26}N_6O_6S_4$: C, 57.06; H, 3.36; N, 10.79. Found: C, 57.00; H, 3.30; N, 10.72.

2-(1,3-Benzodioxol-5-yl)-3-(5-5-[(7-5-[2-(1,3-benzodioxol-5-yl)-4-oxo-1,3-thiazolan-3-yl]-1,3,4-thiadiazol-2-yl-3-methylbenzo[*b*]furan-5-yl)methyl]-3-methylbenzo[*b*]furan-7-yl-1,3,4-thiadiazol-2-yl)-1,3-thiazolan-4-one (5j) This was obtained by reacting **4j** (3.69 g) and thioglycolic acid (1.12 g) as described in the typical procedure and isolated as black solid. Yield 77%, mp 211—213 °C. IR (KBr) cm^{-1}: 3072, 1698, 1612, 1604, 1475, 1066, 1027, 713. ^{1}H-NMR (DMSO-d_6) δ: 7.64 (s, 2H, Ar-H), 7.49 (s, 2H, Ar-H), 7.24 (s, 2H, Ar-H), 7.14 (d, J=7.9 Hz, 2H, Ar-H), 6.98—6.90 (m, 4H, Ar-H), 5.94 (s, 2H, CH), 5.92 (s, 4H, CH_2), 4.20 (s, 2H, CH_2), 3.67 (s, 4H, CH_2), 2.36 (s, 6H, CH_3). ^{13}C-NMR (DMSO-d_6) δ: 173.2, 170.6, 154.6, 150.8, 148.1, 147.9, 142.7, 135.9, 135.2, 132.0, 127.1, 126.9, 125.8, 123.6, 119.7, 118.7, 109.2, 105.3, 72.8, 42.0, 34.0, 9.20. MS m/z: 886 (M^+). *Anal.* Calcd for $C_{43}H_{30}N_6O_8S_4$: C, 58.23; H, 3.41; N, 9.47. Found: C, 58.20; H, 3.36; N, 9.42.

Nematicidal Assay For the nematicidal assay the *D. myceliophagus* was extracted from the cultivated mushrooms (*Agaricus bisporus*) infected with the nematode, and *C. elegans* was grown on 10 cm 8P plates[55] on a *E. coli* NA22 bacteria diet, which grow in a very thick layer and constitute an abundant food source for large quantities on nematode. The nematode water suspension was collected in Petri dishes. Suspension of adult worms from 5 d old culture was diluted with approximately 100 to 250 nematodes/ml of water, 100 μl of the nematode suspension was introduced into a solution of each test compound at various concentrations in a well of 24-well plates and incubated at 25 °C. The percentage of immobile nematodes was recorded after 2 d. The LD_{50} values of the compounds screened are presented in Table 1.

Antibacterial Activity For the antibacterial assay the bacteria were grown over night in Luria Bertani (LB) broth at 37 °C, harvested by centrifugation, and then washed twice with sterile distilled water. Stock solutions of the series of compounds were prepared in DMSO. Each stock solution was diluted with standard method broth (Difco) to prepare serial two-fold dilutions in the range of 50—0.8 μg/ml. Ten microliters of the broth containing about 10^5 colony forming units (cfu)/ml of test bacteria wasere added to each well of 96-well microtiter plate. Culture plates were incubated for 24 h at 37 °C, and the growth was monitored visually and spectrophotometrically.

Antifungal Activity For the antifungal assay the *C. albicans* was grown for 48 h at 28 °C in YPD broth (1% yeast extract, 2% peptone, and 2% dextrose), harvested by centrifugation and then washed twice with sterile distilled water. *A. fumigatus*, *T. rubrum* and *T. mentagrophytes* were plated in potato dextrose agar (PDA) (Difco) and incubated at 28 °C for two weeks. Spores were washed three times with sterile distilled water and resuspended in distilled water to obtain an initial inoculum size of 10^5 spores/ml. Each test compound was dissolved in DMSO and diluted with potato dextrose broth (Difco) to prepare serial two-fold dilutions in the range of 100 to 0.8 μg/ml. Ten microliters of the broth containing about 10^3 (for yeast) and 10^4 (for filamentous fungi) cells/ml of test fungi was added to each well of a 96-well microtiter plate. Culture plates were incubated for 48—72 h at 28 °C.

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