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Design, synthesis, antibacterial and antifungal activity of novel spiro-isoxazolyl bis-[5,5']thiazolidin-4-ones and spiro-isoxazolyl thiazolidin-4-one-[5,5']-1,2-4 oxdiazolines

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Design, synthesis, antibacterial and antifungal activity of novel spiro-isoxazolyl bis-[5,5′]thiazolidin-4-ones and spiro-isoxazolyl thiazolidin-4-one-[5,5′]-1,2-4 oxdiazolines

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The synthesis of novel isoxazolyl 1,6-dithia-4,9-diazaspiro[4.4]nonane-3,8-diones (**4a**–**h**) and isoxazolyl 1-oxa-6-thia-2,4,9-triazaspiro[4.4]non-2-ene-8-ones (**5a**–**h**) analogs is described. Reaction of *N*-1-{3-methyl-5-[(*E*)-2-aryl-1-ethenyl]-4-isoxazolyl}-2-chloroacetamide (**2**) with aryl isothiocyanates yielded 3,3-methyl-5-[(*E*)-2-aryl-1-ethenyl]-4-isoxazolyl-2-(arylimino)-1,3-thiazolan-4-ones (**3**). Cyclocondensation of **3** with mercaptoacetic acid furnished novel isoxazolyl-1,6-dithia-4,9-diazaspiro[4.4]nonane-3,8-diones (**4a**–**h**). Cycloaddition of **3** with benzonitrile oxides afforded novel isoxazolyl 1-oxa-6-thia-2,4,9-triazaspiro[4.4]non-2-ene-8-ones (**5a**–**h**). Compounds **4a**–**h** and **5a**–**h** showed significant biological activity against all the standard strains.

Keywords: cyclocondensation reaction; spirothiazolidinones; cycloaddition reaction; antibacterial activity; antifungal activity

1. Introduction

The importance of heterocycles in biological systems has stimulated interest in designing and constructing new heterocyclic systems using a molecular modification approach. Among various heterocyclic systems, isoxazole holds a prominent role, because it is present as a core unit in a number of compounds possessing a broad spectrum of biological activities (*1*). The chemistry of isoxazole unit continues to draw the attention of synthetic organic chemists, as it constitutes an easily accessible nucleus that is present in a number of natural and pharmacological compounds (*2*).

Isoxazole derivatives are used as potent antitumor (*3*), as CNS-active (*4*), as analgesic (*5*), as antimicrobial (*6*), as muscle relaxant (*7*), for the treatment of hypercholesterolemia and hyperlipidemia (*8*), as organic electrolytes for non-aqueous batteries (*9*), in photographic emulsions (*10*), as synthetic intermediates (*11*) and as chemotherapeutic agents (*12*). Spirothiazolidinones have attracted our attention because of their enhanced activities in medicinal and biological chemistry

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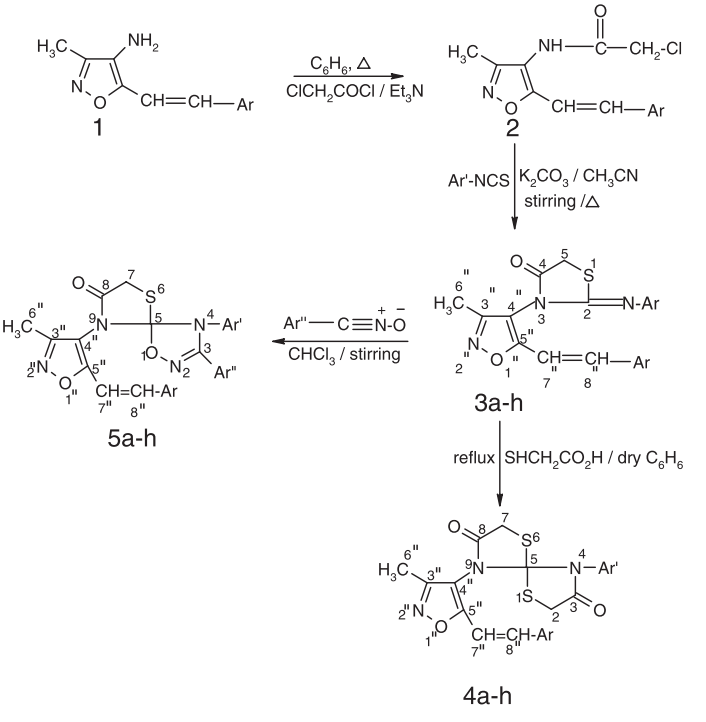
(*13, 14*). Several of these derivatives are known to possess antitubercular (*15*), anticonvulsant (*16*), anti-inflammatory (*17*), fungistatic (*18*), bacteriostatic (*19*) and antimicrobial activity (*20*).

A literature survey revealed that when two heterocyclic moieties are joined together in a single molecular framework, the resulting compound is expected to possess enhanced bioactivity (*21*). Realizing the importance of the above biodynamic heteryl nuclei, and in continuation of our interest in designing the synthesis of biologically active nitrogen and sulfur heterocycles linked to isoxazole ring (*22*), it was thought worthwhile to undertake the synthesis of novel spirothiazolidinones containing isoxazole moiety and to evaluate their antimicrobial activity.

2. Chemistry

The synthesis of compounds **2**, **3**, **4** and **5** was accomplished by the synthetic sequence shown in Scheme 1. The reaction of 4-amino-3-methyl-5-styrylisoxazole (**1**) (*23*) with chloroacetyl chloride in the presence of triethyl amine in benzene furnished *N*-1-{3-methyl-5-[(*E*)-2-aryl-1-ethenyl]-4-isoxazolyl}-2-chloroacetamide (**2**) (*24*). Compound **2** on treatment with aryl isothiocyanates in the presence of K_2CO_3 in CH_3CN afforded the key intermediates, *viz*., 3-3-methyl-5-[(*E*)-2-aryl-1-ethenyl]-4-isoxazolyl-2-(arylimino)-1,3-thiazolan-4-ones (**3**). The mechanism involves the addition of amide derivative to isothiocyanate in the presence of a base and subsequent cyclization takes place by nucleophilic substitution of chlorine by the sulfur atom of isothiocyanate. This mechanism was in agreement with an earlier observation (*25*). Cyclocondensation of **3** with mercaptoacetic acid in dry benzene led to the formation of novel 4-3-{methyl-5[(*E*)-2-aryl-1-ethenyl]-4-isoxazolyl}-9-aryl-1,6-dithia-4,9-diazaspiro[4.4]nonane-3,8-diones (**4**). The other possible regioisomer was not formed in the reaction. This selectivity in the cyclocondensation giving only one of the two possible regioisomers may be ascribed to the polarization of the imine double bond in **3** toward the nitrogen rendering the imine carbon positively charged. So, the mercapto functional group of mercaptoacetic acid makes a nucleophilic attack on the imine carbon giving only **4**. The styryl double bond, which is not polarized, is inert toward the nucleophilic attack of mercaptoacetic acid, hence the chemoselectivity was observed only in the imine group. Cycloaddition of **3** with benzonitrile oxides generated *in situ* from benzhydroxamoyl chloride in the presence of triethyl amine at ice-cold temperature furnished the novel 9-{3-methyl-5[(*E*)-2-phenyl-1-ethenyl]-4-isoxazolyl}-3,4-diphenyl-1-oxa-6-thia-2,4,9-triazaspiro[4.4]non-2-ene-8-ones (**5**) by the 1,3-dipolar cycloaddition (Scheme 1). The other regioisomer could not be obtained in the reaction. This selectivity in cycloaddition leading to the formation of only one of the possible region isomers may be due to the polarization of the imine double bond of **3** toward nitrogen, making imine carbon positively charged. So, the oxygen of benzonitrile oxide attacks on this carbon giving only **5**. When the reaction was performed using excess of benzonitrile oxide, only one regioisomer **5** was obtained, indicating that the olefinic double bond of the styryl moiety is inert, hence the chemoselectivity was achieved with the participation of imine double bond. The structures of products **3**, **4** and **5** have been elucidated on the basis of spectral (IR, ^{1}H NMR, and MS) and microanalytical data.

Compound **3** displayed characteristic absorption bands in the IR spectra around 1630 and 1685 cm^{-1} due to C=N and C=O functional groups, respectively, confirming cyclocondensation. ^{1}H NMR spectra of **3** exhibited a sharp singlet around δ 4.2 due to newly formed thiazolan-4-one ring methylene protons. Mass spectrum of the product **3** agrees well with the cyclized structure, which showed a molecular ion peak at $[M + H]^+$ at m/z 376. The ^{1}H NMR spectrum of **4** displayed two distinct singlets around δ 4.2 and 4.4 due to methylene protons of thiazolidinone rings, confirming the formation of spirothiazolidinone rings. The mass spectrum of **4** confirmed the structure by exhibiting the molecular ion peak $[M + H]^+$ at m/z 450. The ^{1}H NMR spectrum of **5** showed a prominent singlet around 4.0 due to thiazolidinone ring CH_2 protons. The mass spectrum



3,4

Ar	Ar′
a , C_6H_5	C_6H_5
b, 4-$CH_3OC_6H_4$	C_6H_5
c, 4-ClC_6H_4	C_6H_5
d, 2-ClC_6H_4	C_6H_5
e, 4-$CH_3C_6H_4$	4-$CH_3OC_6H_4$
f, C_6H_5	4-Br C_6H_4
g, C_6H_5	4-$CH_3C_6H_4$
h, 4-$CH_3OC_6H_4$	4-ClC_6H_4

5

Ar	Ar′	Ar′′
a , C_6H_5	C_6H_5	C_6H_5
b , 4-$CH_3OC_6H_4$	C_6H_5	C_6H_5
c, 4-ClC_6H_4	C_6H_5	C_6H_5
d, 2-ClC_6H_4	C_6H_5	C_6H_5
e, 4-$CH_3C_6H_4$	4-$CH_3OC_6H_4$	C_6H_5
f, C_6H_5	C_6H_5	4-ClC_6H_4
g, C_6H_5	C_6H_5	4-$CH_3OC_6H_4$
h, C_6H_5	C_6H_5	4-$NO_2C_6H_4$

Scheme 1. Synthesis of spiro-isoxazolyl bis-[5,5′]thiazolidin-4-ones and spiro-isoxazolyl thiazolidin-4-one-[5,5′]-1,2,4-oxazdiazolines.

of **5** also agrees well with the structure, which showed the molecular ion peak $[M + H]^+$ at m/z 495 confirming the cycloaddition reaction. Elemental analyses are satisfactory and confirmed elemental composition and purity of the newly synthesized compounds **3-5**.

3. Antibacterial activity

Antibacterial activity of **4a**–**h** and **5a**–**h** in acetone was performed by the broth dilution method using nutrient agar against Gram-negative bacteria *Pseudomonas aeruginosa*, *Klebsiella*

Table 1. Antibacterial activity of **4a**–**h**.

	Minimum inhibitory concentration					
	Gram-positive			Gram-negative		
Compound	*B. subtilis*	*B. sphaericus*	*S. aureus*	*P. aeruginosa*	*K. aerogenes*	*C. violaceum*
4a	16	21	25	20	18	17
4b	13	12	14	12	9	15
4c	21	18	16	10	16	19
4d	20	23	28	21	18	17
4e	19	19	20	18	15	16
4f	18	13	17	20	12	12
4g	14	17	11	15	14	11
4h	15	22	24	11	11	20
Ciprofloxacin	23	25	30	22	20	22

Notes: Negative control (acetone) – no activity. Values are indicated in μg/ml.

aerogenes, *Chormobacterium violaceum* and Gram-positive bacteria *Bacillus subtilis*, *Bacillus sphaericus* and *Staphylococcus aureus* at 100 μg/ml concentration. The minimum inhibitory concentration was done by the broth dilution method (*26*). Ciprofloxacin was used as standard for comparison. The ready-made nutrient broth medium (Himedia, 24 g) was suspended in distilled water (100 ml) and heated until it dissolved completely. The medium and test tubes were autoclaved at a pressure of 15 lb/inc^2 for 20 min. A set of sterilized test tubes with nutrient broth medium was capped with cotton plugs. The test compound was dissolved in acetone and a concentration of 100 μg/ml of the test compound was added in the first test tube, which was serially diluted. A fixed volume of 0.5 ml of overnight culture was added in all the test tubes which were incubated at 37°C for 24 h. After 24 h, these tubes were measured for turbidity. Results are given in Tables 1 and 2.

The results of antibacterial screening (Tables 1 and 2) reveal that compounds **4a**–**h** and **5a**–**h** displayed a better activity and are more active than the standard drug ciprofloxacin. In series **4**, compounds **4c**, **4f** and **4g** possessing chloro, bromo and methyl groups as substituents on the benzene ring showed a better activity, whereas in series **5**, compounds **5b** and **5f** carrying methoxy and chloro groups as substituents on the benzene ring imparted a remarkable activity. However, the degree of inhibition varied both with the test compound and with the bacteria used in the present investigation. In conclusion, almost all the compounds, **4a**–**h** and **5a**–**h**, exhibited the maximum activity by inhibiting the growth of all the six bacteria to a greater extent in comparison

Table 2. Antibacterial activity of **5a**–**h**.

	Minimum inhibitory concentration					
	Gram-positive			Gram-negative		
Compound	*B. subtilis*	*B. sphaericus*	*S. aureus*	*P. aeruginosa*	*K. aerogenes*	*C. violaceum*
5a	16	15	16	20	16	13
5b	8	11	12	8	13	15
5c	16	15	18	18	15	15
5d	18	17	15	20	18	15
5e	20	16	20	17	19	16
5f	10	8	12	8	13	10
5g	15	15	20	15	15	17
5h	19	17	16	20	17	16
Ciprofloxacin	20	20	25	30	25	25

Notes: Negative control (acetone) – no activity. Values are indicated in μg/ml.

with the standard drug streptomycin. The antibacterial activity of some of these compounds is promising compared with standard ciprofloxacin, and they can be exploited for the formation of bactericide after further study.

4. Antifungal activity

The antifungal activity of **4a**–**h** and **5a**–**h** was performed by the agar cup bioassay method (*27*) using clotrimazole as the standard. The compounds were tested for their antifungal activity against five test organisms, *Aspergillus niger*, *Chrysosporium tropicum*, *Rhizopus oryzae*, *Fusarium moniliforme* and *Curvularia lunata* using the agar cup bioassay method at 100 μg/ml concentration. The ready-made potato dextrose agar medium (Himedia, 39 g) was suspended in distilled water (1000 ml) and heated until it dissolved completely. The medium and Petri dishes were autoclaved at a pressure of 15 lb/inc^2 for 20 min. The medium was poured into sterile Petri dishes under aseptic conditions in a laminar flow chamber. When the medium in the plates solidified, 0.5 ml of the (week-old) culture of test organism was inoculated and uniformly spread over the agar surface with a sterile L-shaped rod. Solutions were prepared by dissolving plant extract in acetone (100 μg/ml). Agar inoculation cups were scooped out with 6 mm sterile cork borer and the lids of the dishes were replaced. To each cup, 100 μg/ml of test solution was added. Controls were maintained with acetone and clotrimazole (100 μg/ml). The treated and the controls were kept at room temperature for 72–96 h. Inhibition zones were measured and the diameter was calculated in millimeters. Three to four replicates were maintained for each treatment. The results are given in Tables 3 and 4.

Table 3. Antifungal activity of **4a**–**h**.

	Zone of inhibition in mm				
Compound	*A. niger*	*C. tropicum*	*R. oryzae*	*F. moniliforme*	*C. lunata*
4a	26	20	15	19	17
4b	50	45	55	50	45
4c	50	55	50	45	40
4d	25	20	25	20	20
4e	26	20	19	18	18
4f	25	24	26	30	35
4g	20	23	23	15	15
4h	30	25	30	20	20
Clotrimazole	29	30	28	23	20

Note: Negative control (acetone) – no activity.

Table 4. Antifungal activity of **5a**–**h**.

	Zone of inhibition in mm				
Compound	*A. niger*	*C. tropicum*	*R. oryzae*	*F. moniliforme*	*C. lunata*
5a	45	45	35	35	40
5b	50	55	55	55	55
5c	30	40	30	35	40
5d	50	55	40	50	45
5e	40	50	55	50	50
5f	45	40	35	40	45
5g	35	35	40	45	45
5h	55	55	55	55	50
Clotrimazole	26	29	23	27	28

Note: Negative control (acetone) – no activity.

The antifungal activity results (Tables 3 and 4) indicated that compounds **4a**–**h** and **5a**–**h** are significantly toxic toward all the five fungi and they are lethal at 100 μg/ml concentration. In series **4**, compounds **4b** and **4c** exhibited a high antifungal activity which may be due to the presence of methoxy and chloro substituents on the benzene ring. In series **5**, compounds **5b** and **5h** possessing methoxy and nitro groups are highly toxic toward some fungi. However, the degree of spore germination inhibited varied with the test compound as well as with the fungi. The antifungal activity of these compounds was compared with the standard drug clotrimazole, and they have a promising activity, when compared with the standard drug. In conclusion, almost all the series of compounds, **4a**–**h** and **5a**–**h**, are highly toxic toward the fungi under investigation and they are lethal even at 100 μg/ml concentration in comparison with standard clotrimazole at the same concentration. It is noteworthy that some of the compounds may be exploited for control of wilt diseases of different crops as fungicides after detailed study.

5. Experimental

Melting points were recorded on an Electrothermal type 9100 melting point apparatus and are uncorrected. The IR spectra were recorded on Nicolet Impact 410 FTIR spectrophotometer using KBr pellets. ^{1}H NMR spectra were recorded on Bruker Ac 300 spectrometer in $CDCl_3$ and with TMS as the internal standard. The mass spectra were obtained on a Varian MATCH-7 instrument at 70 eV. Elemental analyses were carried out using Perkin-Elmer 240C CHN-analyzer.

5.1. *Synthesis of 3-3-methyl-5-[(E)-2-aryl-1-ethenyl]-4-isoxazolyl-2-(arylimino)-1,3-thiazolan-4-one derivatives (3a–h) – general procedure*

A mixture of *N*-1-{3-methyl-5[(*E*)-2-aryl-1-ethenyl]-4-isoxazolyl}-2-chloroacetamide (**2**) (0.01 mol) and aryl isothiocyanate (0.01 mol) was taken in acetonitrile (15 ml) in the presence of K_2CO_3 (0.5 g). The reaction mixture was refluxed while stirring for about 6 h. The solvent was removed under reduced pressure and the residue was purified by recrystallization from methanol to produce **3a**–**h** in high yields.

5.2. *3-{3-Methyl-5-[(E)-2-aryl-1-ethenyl]-4-isoxazolyl}-2-(arylimino)-1,3-thiazolan-4-one (3a)*

Pale yellow powder; yield 85%, m.p. 180–181°C; IR (KBr) cm^{-1}: 1630 (C=N), 1685 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.32 (s, 3H, CH_3), 4.30 (s, 2H, CH_2), 6.82, 7.20 (2d, $J = 15.2$ Hz, 2H, CH=CH), and 7.35–8.03 (m, 10H, ArH). EI-MS[M + H]$^+$ m/z 376. ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 11.41 (C-6″), 28.35 (C-5), 109.87 (C-7″), 115.20 (C-8″), 115.27 (C-4″), 120.10 (Ar–C), 126.87 (Ar–C), 127.35 (Ar–C), 127.81 (Ar–C), 129.01 (Ar–C), 130.25 (Ar–C), 130.88 (Ar–C), 132.29 (Ar–C), 134.65 (Ar–C), 137.69 (Ar–C), 138.39 (Ar–C), 141.09 (Ar–C), 156.28 (C-3″), 158.85 (C-5″), 160.70 (C-2), 174.60 (C-4). Anal. Calcd. for $C_{21}H_{17}N_3O_2S$ (375.45): C, 67.20; H, 4.53; N, 11.20. Found: C, 67.17; H, 4.49; N, 11.16%.

5.3. *3-{5-[(E)-2-(4-Methoxyphenyl)-1-ethenyl]-3-methyl-4-isoxazolyl}-2-(phenylimino)-1,3-thiazolan-4-one (3b)*

Pale yellow powder; yield 85%, m.p. 130–131°C; IR (KBr) cm^{-1}: 1620 (C=N), 1685 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.40 (s, 3H, CH_3), 3.82 (s, 3H, OCH_3), 4.10 (s, 2H, CH_2), 6.76, 7.35 (2d, $J = 15.2$ Hz, 2H, CH=CH), and 7.30–8.22 (m, 9H, ArH). EI-MS [M + H]$^+$ m/z 406. ^{13}C

NMR (75 MHz, $CDCl_3$) δ (ppm): 11.39 (C-6″), 31.50 (C-5), 53.05 (Ar–OCH_3), 109.87 (C-7″), 114.85 (C-8″), 115.05 (C-4″), 119.25 (Ar–C), 125.56 (Ar–C), 126.65 (Ar–C), 127.85 (Ar–C), 129.50 (Ar–C), 130.55 (Ar–C), 131.00 (Ar–C), 132.85 (Ar–C), 133.95 (Ar–C), 137.10 (Ar–C), 138.05 (Ar–C), 142.05 (Ar–C), 155.25 (C-5″), 159.56 (C-3″), 165.33 (C-2), 185.50 (C-4). Anal. Calcd. for $C_{22}H_{19}N_3O_3S$ (405.47): C, 65.18; H, 4.69; N, 10.37. Found: C, 65.17; H, 4.67; N, 10.32%.

5.4. *3-{5-[(E)-2-(4-Chlorophenyl)-1-ethenyl]-3-methyl-4-isoxazolyl}-2-(phenylimino)-1,3-thiazolan-4-one (3c)*

Pale yellow powder; yield 85%, m.p. 145–146°C; IR (KBr) cm^{-1}: 1615 (C=N), 1690 (C=O); ^1H NMR (300 MHz, $CDCl_3$) δ: 2.33 (s, 3H, CH_3), 4.31 (s, 2H, CH_2), 6.90, 7.25 (2d, J = 15.2 Hz, 2H, CH=CH), and 7.40–8.12 (m, 9H, ArH); EI-MS $[M + H]^+$ m/z 410. Anal. Calcd. for $C_{21}H_{16}N_3O_2SCl$ (409.89): C, 61.61; H, 3.91; N, 10.26. Found: C, 61.57; H, 3.89; N, 10.21%.

5.5. *3-{5-[(E)-2-(2-Chlorophenyl)-1-ethenyl]-3-methyl-4-isoxazolyl}-2-(phenylimino)-1,3-thiazolan-4-one (3d)*

Pale yellow powder; yield 90%, m.p. 185–186°C; IR (KBr) cm^{-1}: 1625 (C=N), 1695 (C=O); ^1H NMR (300 MHz, $CDCl_3$) δ: 2.22 (s, 3H, CH_3), 4.23 (s, 2H, CH_2), 7.05, 7.36 (2d, J = 15.2 Hz, 2H, CH=CH), and 7.48–8.26 (m, 9H, ArH); EI-MS $[M + H]^+$ m/z 410. Anal. Calcd. for $C_{21}H_{16}N_3O_2SCl$ (409.89): C, 61.61; H, 3.91; N, 10.26. Found: C, 61.59; H, 3.87; N, 10.22%.

5.6. *2-[(4-Methoxyphenyl)imino]-3-{3-methyl-5-[(E)-2-(4-methylphenyl)-1-ethenyl]-4-isoxazolyl}-1,3-thiazolan-4-one (3e)*

Pale yellow powder; yield 80%, m.p. 175–176°C; IR (KBr) cm^{-1}: 1625 (C=N), 1680 (C=O); ^1H NMR (300 MHz, $CDCl_3$) δ: 2.30 (s, 3H, CH_3), 2.52 (s, 3H, CH_3), 3.71 (s, 3H, OCH_3), 4.33 (s, 2H, CH_2), 6.62, 7.25 (2d, J = 15.2 Hz, 2H, CH=CH), and 7.33–8.05 (m, 8H, ArH). EI-MS $[M + H]^+$ m/z 420. Anal. Calcd. for $C_{23}H_{21}N_3O_3S$ (419.50): C, 65.87; H, 5.01; N, 10.02. Found: C, 65.82; H, 5.00; N, 10.01%.

5.7. *2-[(4-Bromophenyl)imino]-3-{3-methyl-5-[(E)-2-phenyl)-1-ethenyl]-4-isoxazolyl}-1,3-thiazolan-4-one (3f)*

Pale yellow powder; yield 85%, m.p. 170–171°C; IR (KBr) cm^{-1}: 1615 (C=N), 1680 (C=O); ^1H NMR (300 MHz, $CDCl_3$) δ: 2.35 (s, 3H, CH_3), 4.35 (s, 2H, CH_2), 6.82, 7.25 (2d, J = 15.2 Hz, 2H, CH=CH), and 7.22–8.14 (m, 9H, ArH). EI-MS $[M + H]^+$ m/z 454. Anal. Calcd. for $C_{21}H_{16}N_3O_2SBr$ (454.34): C, 55.62; H, 3.53; N, 9.27. Found: C, 55.60; H, 3.50; N, 9.23%.

5.8. *3-{3-Methyl-5-[(E)-2-phenyl-1-ethenyl]-4-isoxazolyl}-2-[(4-methylphenyl)imino]-1,3-thiazolan-4-one (3g)*

Pale yellow powder; yield 80%, m.p. 165–166°C; IR (KBr) cm^{-1}: 1640 (C=N), 1700 (C=O); ^1H NMR (300 MHz, $CDCl_3$) δ: 2.35 (s, 3H, CH_3), 2.52 (s, 3H, CH_3), 4.25 (s, 2H, CH_2), 6.77, 7.32 (2d, J = 15.2 Hz, 2H, CH=CH), 7.48–8.18 (m, 9H, ArH); EI-MS $[M + H]^+$ m/z 390. Anal. Calcd. for $C_{22}H_{19}N_3O_2S$ (389.47): C, 67.86; H, 4.88; N, 10.79. Found: C, 67.84; H, 4.84; N, 10.75%.

5.9. *2-[(4-Chlorophenyl)imino]-3-{-5-[(E)-2-(4-methoxyphenyl)-1-ethenyl]-3-methyl-4-isoxazolyl}-1,3-thiazolan-4-one (3h)*

Pale yellow powder; yield 85%, m.p. 195–196°C; IR (KBr) cm^{-1}: 1638 (C=N), 1680 (C=O); ^1H NMR (300 MHz, $CDCl_3$) δ: 2.40 (s, 3H, CH_3), 3.82 (s, 3H, OCH_3), 4.12 (s, 2H, CH_2), 6.75, 7.12 (2d, $J = 15.2$ Hz, 2H, CH=CH), and 7.13–8.26 (m, 8H, ArH). EI-MS $[M + H]^+$ m/z 440. Anal. Calcd. for $C_{22}H_{18}N_3O_3SCl$ (439.92): C, 60.13; H, 4.10; N, 9.56. Found: C, 60.10; H, 4.08; N, 9.52%.

5.10. *4-{3-Methyl-5-[(E)-2-aryl-1-ethenyl]-4-isoxazolyl}-9-aryl-1,6-dithia-4,9-diazaspiro [4.4]nonane-3,8-dione derivatives (4a–h) – general procedure*

To a solution of 3-3-methyl-5-[(*E*)-2-aryl-1-ethenyl]-4-isoxazolyl-2-(arylimino)-1,3-thiazolan-4-ones (**3**) (0.01 mol) in dry benzene (25 ml) mercaptoacetic acid (0.01 mol) was added and the contents were refluxed in a Dean-stark apparatus for 6 h. The solvent was distilled off and the gummy material obtained was triturated with light petrol repeatedly. The product was purified by passing through column. Elution with petroleum ether–benzene (1:1) yielded compounds **4a**–**h**.

5.11. *4-{3-Methyl-5-[(E)-2-aryl-1-ethenyl]-4-isoxazolyl}-9-aryl-1,6-dithia-4,9-diazaspiro[4.4]nonane-3,8-dione (4a)*

White powder; yield 70%, m.p. 210–211°C; IR (KBr) cm^{-1}: 1710 (C=O), 1275 (C–S); ^1H NMR (300 MHz, $CDCl_3$) δ: 2.25 (s, 3H, CH_3), 4.20 (s, 2H, CH_2), 4.42 (s, 2H, CH_2), 6.85 (d, J = 15.2 Hz, 1H, CH=CH), 7.22–7.86 (m, 10H, ArH and 1H, CH=CH). EI-MS $[M + H]^+$ m/z 450. ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 11.05 (C-6″), 27.80 (C-2), 28.33 (C-7), 80.05 (C-5), 109.20 (C-4″), 109.90 (C-7″), 115.55 (C-8″), 120.08 (Ar–C), 125.11 (Ar–C), 125.85 (Ar–C), 127.30 (Ar–C), 127.99 (Ar–C), 128.05 (Ar–C), 128.52 (Ar–C), 129.15 (Ar–C), 130.00 (Ar–C), 130.10 (Ar–C), 134.60 (Ar–C), 139.02 (Ar–C), 156.65 (C-5?), 158.90 (C-3?), 176.35 (C-3), 177.05 (C-8). Anal. Calcd. for $C_{23}H_{19}N_3O_3S_2$ (449.55): C, 61.46; H, 4.23; N, 9.35. Found: C, 61.44; H, 4.20; N, 9.32%.

5.12. *4-{5-[(E)-2-(4-Methoxyphenyl)-1-ethenyl]-3-methyl4-isoxazolyl}-9-phenyl-1,6-dithia-4,9-diazaspiro[4.4]nonane-3,8-dione (4b)*

White powder; yield 65%, m.p. 225–226°C; IR (KBr) cm^{-1}: 1720 (C=O), 1280 (C–S); ^1H NMR (300 MHz, $CDCl_3$) δ: 2.22 (s, 3H, CH_3), 3.78 (s, 3H, OCH_3), 4.20 (s, 2H, CH_2), 4.41 (s, 2H, CH_2), 6.73 (d, $J = 15.2$ Hz, 1H, CH=CH), 7.35-7.89 (m, 9H, ArH and 1H, CH=CH). EI-MS $[M + H]^+$ m/z 480. ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 11.45 (C-6″), 27.88 (C-2), 28.53 (C-7), 52.30 (Ar–OCH_3), 81.33 (C-5), 109.55 (C-4″), 109.85 (C-7″), 116.03 (C-8″), 120.09 (Ar–C), 125.05 (Ar–C), 126.00 (Ar–C), 127.15 (Ar–C), 127.85 (Ar–C), 128.02 (Ar–C), 128.63 (Ar–C), 129.15 (Ar–C), 130.08 (Ar–C), 133.15 (Ar–C), 135.00 (Ar–C), 139.07 (Ar–C), 157.05 (C-5″), 158.80 (C-3″), 176.55 (C-3), 178.00 (C-8). Anal. Calcd. for $C_{24}H_{21}N_3O_4S_2$ (479.58): C, 60.12; H, 4.38; N, 8.76. Found: C, 60.09; H, 4.35; N, 8.74%.

5.13. *4-{5-[(E)-2-(4-Chlorophenyl)-1-ethenyl]-3-methyl-4-isoxazolyl}-9-phenyl-1,6-dithia-4,9-diazaspiro[4.4]nonane-3,8-dione (4c)*

White powder; Yield 70%, m.p. 215–216°C; IR (KBr) cm^{-1}: 1730 (C=O), 1270 (C–S); ^1H NMR (300 MHz, $CDCl_3$) δ: 2.30 (s, 3H, CH_3), 4.03 (s, 2H, CH_2), 4.25 (s, 2H, CH_2), 6.9 (d,

$J = 15.2$ Hz, 1H, CH=CH), 7.25–7.96 (m, 9H, ArH and 1H, CH=CH); EI-MS $[M + H]^+$ m/z 484. Anal. Calcd. for $C_{23}H_{18}N_3O_3S_2Cl$ (484.00): C, 57.14; H, 3.72; N, 8.69. Found: C, 57.12; H, 3.70; N, 8.65%.

5.14. *4-{5-[(E)-2-(2-Chlorophenyl)-1-ethenyl]-3-methyl-4-isoxazolyl}-9-phenyl-1,6-dithia-4,9-diazaspiro[4.4]nonane-3,8-dione (4d)*

White powder; yield 70%, m.p. 212–213°C; IR (KBr) cm^{-1}: 1715 (C=O), 1275 (C–S); ^1H NMR (300 MHz, $CDCl_3$) δ: 2.23 (s, 3H, CH_3), 4.20 (s, 2H, CH_2), 4.43 (s, 2H, CH_2), 7.06 (d, $J = 15.2$ Hz, 1H, CH=CH), 7.18–8.18 (m, 9H, ArH and 1H, CH=CH); EI-MS $[M + H]^+$ m/z 484. Anal. Calcd. for $C_{23}H_{18}N_3O_3S_2Cl$ (484.00): C, 57.14; H, 3.72; N, 8.69. Found: C, 57.09; H, 3.69; N, 8.63%.

5.15. *4-(4-Methoxyphenyl)-9-{3-methyl-5-[(E)-2-(4-methylphenyl)-1-ethenyl]-4-isoxazolyl}-1,6-dithia-4,9-diazaspiro[4.4]nonane-3,8-dione (4e)*

White powder; yield 68%, m.p. 235–236°C; IR (KBr) cm^{-1}: 1710 (C=O), 1280 (C–S); ^1H NMR (300 MHz, $CDCl_3$) δ: 2.25 (s, 3H, CH_3), 2.51 (s, 3H, CH3), 3.80 (s, 3H, OCH_3), 4.12 (s, 2H, CH_2), 4.32 (s, 2H, CH_2), 7.05 (d, $J = 15.2$ Hz, 1H, CH=CH), 7.26–8.17 (m, 8H, ArH and 1H, CH=CH). EI-MS $[M + H]^+$ m/z 494. Anal. Calcd. for $C_{25}H_{23}N_3O_4S_2$ (493.60): C, 60.85; H, 4.66; N, 8.51. Found: C, 60.82; H, 4.63; N, 8.48%.

5.16. *4-(4-Bromophenyl)-9-{3-methyl-5-[(E)-2-phenyl-1-ethenyl]-4-isoxazolyl}-1,6-dithia-4,9-diazaspiro[4.4]nonane-3,8-dione (4f)*

White powder; yield 65%, m.p. 240–241°C; IR (KBr) cm^{-1}: 1715 (C=O), 1270 (C–S); ^1H NMR (300 MHz, $CDCl_3$) δ: 2.30 (s, 3H, CH_3), 4.32 (s, 2H, CH_2), 4.50 (s, 2H, CH_2), 6.8 (d, $J = 15.2$ Hz, 1H, CH=CH) and 7.2–8.0 (m, 9H, ArH and 1H, CH=CH). EI-MS $[M + H]^+$ m/z 528. Anal. Calcd. for $C_{23}H_{18}N_3O_3S_2Br$ (528.45): C, 52.37; H, 3.41; N, 7.96. Found: C, 52.33; H, 3.38; N, 7.94%.

5.17. *4-(4-Methylphenyl)-9-{3-methyl-5-[(E)-2-phenyl-1-ethenyl]-4-isoxazolyl}-1,6-dithia-4,9-diazaspiro[4.4]nonane-3,8-dione (4g)*

White powder; yield 70%, m.p. 232–233°C; IR (KBr) cm^{-1}: 1715 (C=O), 1275 (C–S); ^1H NMR (300 MHz, $CDCl_3$) δ: 2.32 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 4.15 (s, 2H, CH_2), 4.30 (s, 2H, CH_2), 6.76 (d, J= 15.2 Hz, 1H, CH=CH) and 7.35–7.95 (m, 9H, ArH and 1H, CH=CH). EI-MS $[M + H]^+$ m/z 464. Anal. Calcd. for $C_{24}H_{21}N_3O_3S_2$ (463.58): C, 62.20; H, 4.53; N, 9.07. Found: C, 62.18; H, 4.51; N, 9.05%.

5.18. *4-(4-Chlorophenyl)-9-{5-[(E)-2-(4-methoxyphenyl)-1-ethenyl]-3-methyl-4-isoxazolyl}-1,6-dithia-4,9-diazaspiro[4.4]nonane-3,8-dione (4h)*

White powder; yield 65%, m.p. 239–240°C; IR (KBr) cm^{-1}: 1720 (C=O), 1275 (C–S); ^1H NMR (300 MHz, $CDCl_3$) δ: 2.25 (s, 3H, CH_3), 3.82 (s, 3H, OCH_3), 4.12 (s, 2H, CH_2), 4.40 (s, 2H, CH_2), 6.65 (d, $J = 15.2$ Hz, 1H, CH=CH) and 7.32–7.85 (m, 8H, ArH and 1H, CH=CH). EI-MS $[M + H]^+$ m/z 514. Anal. Calcd. for $C_{24}H_{20}N_3O_4S_2Cl$ (514.02): C, 56.14; H, 3.89; N, 8.18. Found: C, 56.10; H, 3.86; N, 8.15%.

5.19. *Synthesis of 9-{3-methyl-5-[(E)-2-phenyl-1-ethenyl]-4-isoxazolyl}-3,4-diphenyl-1-oxa-6-thia-2,4,9-triazaspiro[4.4]non-2-en-8-one derivatives (5a-h) – general procedure*

To a solution of 3-3-methyl-5-[(*E*)-2-aryl-1-ethenyl]-4-isoxazolyl-2-(arylimino)-1,3-thiazolan-4-one (**3**) (0.01 mol) in dry chloroform (50 ml), cooled in ice-salt bath, a solution of benzhydroxamoyl chloride (0.01 mol) in chloroform (10 ml) was added. Triethyl amine (0.01 mol) in chloroform (10 ml) was added to the reaction mixture at 0°C for 15 min with constant stirring. After the addition was completed, the stirring was continued for another 4 h at 0°C. The chloroform layer was washed with water (2 × 25 ml) to make it free from triethyl amine hydrochloride and the organic layer was dried (Na_2SO_4). The solvent was removed at ambient temperature and the crude product triturated with light petrol repeatedly to obtain a residue. The residue on shaking with methanol gave the solid, which was recrystallized from benzene.

5.20. *9-{3-Methyl-5-[(E)-2-phenyl-1-ethenyl]-4-isoxazolyl}-3,4-diphenyl-1-oxa-6-thia-2,4,9-triazaspiro[4.4]non-2-en-8-one (5a)*

White powder; yield 78%, m.p. 202–204°C; IR (KBr) cm^{-1}: 1630 (C=N), 1680 (C=O); ^1H NMR (300 MHz, $CDCl_3$) δ: 2.25 (s, 3H, CH_3), 4.05 (s, 2H, CH_2), 6.82 (d, $J = 15.2$ Hz, 1H, CH=CH), 7.25–7.59 (m, 15H, ArH and 1H, CH=CH). EI-MS $[M + H]^+$ m/z 495. ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 11.50 (C-6″), 26.50 (C-7), 100.05 (C-5), 105.68 (C-4″), 110.15 (C-7″), 118.40 (C-8″), 120.10 (Ar–C), 121.85 (Ar–C), 125.10 (Ar–C), 126.88 (Ar–C), 127.35 (Ar–C), 127.81 (Ar–C), 129.01 (Ar–C), 129.29 (Ar–C), 130.25 (Ar–C), 130.65 (Ar–C), 130.88 (Ar–C), 132.29 (Ar–C), 132.80 (Ar–C), 134.65 (Ar–C), 136.32 (Ar–C), 137.67 (Ar–C), 138.39 (Ar–C), 150.07 (C-3), 156.22 (C-3″), 158.90 (C-5″), 169.05 (C-8). Anal. Calcd. for $C_{28}H_{22}N_4O_3S$ (494.57): C, 68.01; H, 4.45; N, 11.33. Found: C, 68.03; H, 4.48; N, 11.30%.

5.21. *9-{-5-[(E)-2-(4-Methoxyphenyl)-1-ethenyl]-3-methyl-4-isoxazolyl}-3,4-diphenyl-1-oxa-6-thia-2,4,9-triazaspiro[4.4] non-2-en-8-one (5b)*

White powder; yield 67%, m.p. 223–224°C; IR (KBr) cm^{-1}: 1640 (C=N), 1680 (C=O); ^1H NMR (300 MHz, $CDCl_3$) δ: 2.32 (s, 3H, CH_3), 3.78 (s, 3H, OCH_3), 4.31 (s, 2H, CH_2), 6.72 (d, $J = 15.2$ Hz, 1H, CH=CH), 7.15–7.40 (m, 14H, ArH and 1H, CH=CH); EI-MS $[M + H]^+$ m/z 525. ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 11.44 (C-6″), 27.05 (C-7), 55.00 (Ar–OCH_3), 100.08 (C-5), 106.01 (C-4″), 111.20 (C-7″), 119.50 (C-8″), 120.05 (Ar–C), 120.98 (Ar–C), 124.85 (Ar–C), 126.05 (Ar–C), 127.55 (Ar–C), 128.00 (Ar–C), 129.33 (Ar–C), 129.55 (Ar–C), 130.08 (Ar–C), 131.04 (Ar–C), 133.00 (Ar–C), 132.60 (Ar–C), 135.02 (Ar–C), 136.65 (Ar–C), 137.80 (Ar–C), 138.44 (Ar–C), 140.05 (Ar–C), 141.08 (Ar–C), 151.05 (C-3), 155.23 (C-3″), 158.88 (C-5″), 170.05 (C-8). Anal. Calcd. for $C_{29}H_{24}N_4O_4S$ (524.60): C, 66.41; H, 4.58; N, 10.70. Found: C, 66.39; H, 4.55; N, 10.67%.

5.22. *9-{-5-[(E)-2-(4-Chlorophenyl)-1-ethenyl]-3-methyl-4-isoxazolyl}-3,4-diphenyl-1-oxa-6-thia-2,4,9-triazaspiro[4.4]non-2-en-8-one (5c)*

White powder; yield 73%, m.p. 211–212°C; IR (KBr) cm^{-1}: 1635 (C=N), 1685 (C=O); ^1H NMR (300 MHz, $CDCl_3$) δ: 2.25 (s, 3H, CH_3), 4.22 (s, 2H, CH_2), 6.80 (d, $J = 15.2$ Hz, 1H, CH=CH), 7.3–8.0 (m, 14H, ArH and 1H, CH=CH); EI-MS $[M + H]^+$ m/z 529. Anal. Calcd. for $C_{28}H_{21}N_4O_3SCl$ (529.02): C, 63.63; H, 3.97; N, 10.60. Found: C, 63.60; H, 3.95; N, 10.58%.

5.23. *Synthesis of 9-{-5-[(E)-2-(2-chlorophenyl)-1-ethenyl]-3-methyl-4-isoxazolyl}-3,4-diphenyl-1-oxa-6-thia-2,4,9-triazaspiro[4.4]non-2-en-8-one (5d)*

Yield 78%, m.p. 208–209°C; IR (KBr) cm^{-1}: 1640 (C=N), 1670 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.25 (s, 3H, CH_3), 4.30 (s, 2H, CH_2), 6.70 (d, $J = 15.2$ Hz, 1H, CH=CH), 7.22–7.80 (m, 14H, ArH and 1H, CH=CH); EI-MS $[M + H]^+$ m/z 529. Anal. Calcd. for $C_{28}H_{21}N_4O_3SCl$ (529.02): C, 63.63; H, 3.97; N, 10.60. Found: C, 63.66; H, 3.99; N, 10.63%.

5.24. *4-(4-Methoxyphenyl)-9-{-3-methyl-5[(E)-2-(4-methoxyphenyl)-1-ethenyl]-4-isoxazolyl}-3-phenyl-1-oxa-6-thia-2,4,9-triazaspiro[4.4] non-2-en-8-one (5e)*

White powder; yield 65%, m.p. 229–230°C; IR (KBr) cm^{-1}: 1635 (C=N), 1675 (C=O); ^{1}HNMR (300 MHz, $CDCl_3$) δ: 2.23 (s, 3H, CH_3), 2.55 (s, 3H, CH3), 3.80 (s, 3H, OCH3), 4.22 (s, 2H, CH_2), 6.80 (d, $J = 15.2$ Hz, 1H, CH=CH), 7.15–7.93 (m, 13H, ArH and 1H, CH=CH); EI-MS $[M + H]^+$ m/z 523. Anal. Calcd. for $C_{30}H_{26}N_4O_3S$ (522.62): C, 68.91; H, 4.83; N, 10.60. Found: C, 66.87; H, 4.86; N, 10.58%.

5.25. *3-(4-Chlorophenyl)-9-{3-methyl-5[(E)-2-phenyl-1-ethenyl]-4-isoxazolyl-4-phenyl-1-oxa-6-thia-2,4,9-triazaspiro[4.4]non-2-en-8-one (5f)*

White powder; yield 68%, m.p. 232–233°C; IR (KBr) cm^{-1}: 1635 (C=N), 1695 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.35 (s, 3H, CH_3), 4.12 (s, 2H, CH_2), 6.72 (d, $J = 15.2$ Hz 1H, CH=CH) and 7.22–8.14 (m, 14H, ArH and 1H, CH=CH) EI-MS $[M + H]^+$ m/z 529. Anal. Calcd. for $C_{28}H_{21}N_4O_3SCl$ (529.02): C, 63.63; H, 3.97; N, 10.60. Found: C, 63.58; H, 3.94; N, 10.58%.

5.26. *3-(4-Methoxyphenyl)-9-{-3-methyl-5[(E)-2-phenyl-1-ethenyl]-4-isoxazolyl}-4-phenyl-1-oxa-6-thia-2,4,9-triazaspiro[4.4]non-2-en-8-one (5g)*

Yield 72%, m.p. 225–226°C; IR (KBr) cm^{-1}: 1640 (C=N), 1680 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.20 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 4.15 (s, 2H, CH_2), 6.62 (d, $J = 15.2$ Hz, 1H, CH=CH), 7.32–7.95 (m, 14H, ArH and 1H, CH=CH); EI-MS $[M + H]^+$ m/z 524. Anal. Calcd. for $C_{29}H_{24}N_4O_4S$ (524.60): C, 66.41; H, 4.58; N, 10.68. Found: C, 66.43; H, 4.55; N, 10.70%.

5.27. *9-{3-Methyl-5-[(E)-2-phenyl-1-ethenyl]-4-isoxazolyl}-3-(4-nitrophenyl)-4-phenyl-1-oxa-6-Thia-2,4,9-triazaspiro[4.4] non-2-en-8-one (5h)*

White powder; yield 70%, m.p. 235–236°C; IR (KBr) cm^{-1}: 1635 (C=N), 1695 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.25 (s, 3H, CH_3), 4.22 (s, 2H, CH_2), 6.80 (d, $J = 15.2$ Hz, 1H, CH=CH), 7.22–7.85 (m, 14H, ArH and 1H, CH=CH); EI-MS $[M + H]^+$ m/z 540. Anal. Calcd. for $C_{28}H_{21}N_5O_5S$ (539.57): C, 62.33; H, 3.89; N, 12.98. Found: C, 62.34; H, 3.86; N, 12.95%.

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