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Synthesis of 3-[4-({Methyl-5-[(*E*)-2-phenyl-1-ethenyl]-4-isoxazolyl}amino)-1,3-thiazol-2-yl]-2-aryl-1,3-thiazolan-4-ones as Potential Biodynamic Agents

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Synthesis of 3-[4-({Methyl-5-[(*E*)-2-phenyl-1-ethenyl]-4-isoxazolyl}amino)-1,3-thiazol-2-yl]-2-aryl-1,3-thiazolan-4-ones as Potential Biodynamic Agents

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*A series of isoxazolyl thiazolyl thiazolidinones (4a–h) were synthesized starting from isoxazolyl chloroacetamide 1. Compound 1 upon heating with thiourea in ethanol furnished N4-{3-methyl-5-[(*E*)-2-phenyl-1-ethenyl]-4-isoxazolyl]-1,3-thiazole-2,4-diamine 2. Condensation of 2 with aromatic aldehydes afforded corresponding Schiff bases (3a–h), which undergo cyclocondensation on treatment with mercaptoacetic acid to give 3-[4-({methyl-5-(*E*)-2-phenyl-1-ethenyl]-4-isoxazolyl}amino)-1,3-thiazol-2-yl]-2-aryl-1, 3-thiazolyl -4-ones (4a–h) in excellent yields. Structures of all the synthesized compounds have been established by elemental analyses, IR, ¹H NMR, and mass spectral data.*

Keywords Isoxazolyl thiazoles; isoxazolyl thiazolyl Schiff bases; isoxazolyl thiazolyl thiazolidinones

INTRODUCTION

The importance of heterocyclic compounds has long been recognized in the field of synthetic organic chemistry. It is well-known that a number of heterocyclic compounds containing nitrogen and sulfur exhibit a variety of biological activities.^{1–4} Heterocycles bearing isoxazole, thiazole, and thiazolidinones have been found to be associated with diverse pharmacological activities. The chemistry of isoxazole derivatives continues to draw the attention of synthetic organic chemists due to their varied biological activities.⁵ Several of these derivatives are potent antitumor,⁶ CNS-active,⁷ analgesic,⁸ antimicrobial,⁹ and chemotherapeutic agents.¹⁰ Thiazole derivatives have been employed as antipsychotics,¹¹ antimalarials,¹² antibacterials,¹³ and antiparasitics.¹⁴ Thiazolidinones have occupied a

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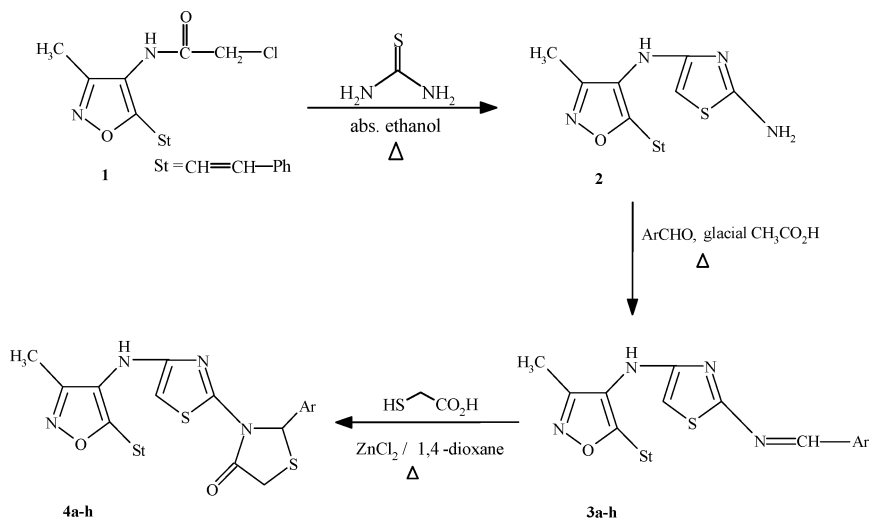
unique place, and they have been found to be associated with diverse pharmacological activities, such as antimicrobial,¹⁵ antihistamic,¹⁶ anti-inflammatory, analgesic, and anticonvulsants.¹⁷ In addition, thiazolidinones have been proven as calcium antagonists with both calcium overload inhibition and antioxidant activity.¹⁸

A survey of the literature reveals that when one biodynamic heterocyclic system was coupled with another, a molecule with enhanced biological activity^{19,20} was produced. The chemistry of these linked heterocycles has been a fascinating field of investigation in medicinal chemistry, as they have been found to exhibit enhanced biological profiles.²¹ In continuation of our interest in designing the synthesis of biologically active heterocycles containing an isoxazole unit,^{22–27} the synthesis of some new biologically active 3-[4-(methyl-5-[(*E*)-2-phenyl-1-ethenyl]-4-isoxazolyl) amino]-1,3-thiazol-2-yl]-2-aryl-1,3-thiazolan-4-ones has been undertaken.

RESULTS AND DISCUSSION

The synthetic scheme of compounds **4a–h** is shown in Scheme 1. The starting material used in this synthesis, *N*1-{3-methyl-5-[(*E*)-2-phenyl-1-ethenyl]-4-isoxazolyl}-2-chloroacetamide (**1**),²⁸ has been prepared by the interaction of 4-amino-3-methyl 5-styrylisoxazole with chloroacetyl chloride in the presence of E_3N in dry benzene. The isoxazolyl chloroacetamide (**1**), on heating with thiourea in ethanol, furnished *N*4-{3-methyl-5-[(*E*)-2-phenyl-1-ethenyl]-4-isoxazolyl}-1,3-thiazole-2,4-diamine (**2**). Condensation of (**2**) with aromatic aldehydes in the presence of glacial acetic acid in ethanol afforded the corresponding Schiff bases, *viz.*, *N*4-{3-methyl-5-[(*E*)-2-phenyl-1-ethenyl]-4-isoxazolyl}-*N*2-[(*E*)-1-arylmethylidene]-1,3-thiazole-2,4-diamines (**3a–h**). The Schiff bases (**3**) upon cyclocondensation with mercaptoacetic acid in refluxing dioxane in the presence of anhydrous $ZnCl_2$ led to the formation of 3-[4-(methyl-5-(*E*)-2-phenyl-1-ethenyl)-4-isoxazolyl] amino)-1,3-thiazol-2-yl]-2-aryl-1,3-thiazolan-4-ones (**4a–h**) in excellent yields (Scheme 1).

Structures of new compounds (**2**), (**3**), and (**4**) were confirmed by their spectral and micro-analytical data. Disappearance of the carbonyl group absorption at 1675 cm^{-1} in the IR spectrum of (**2**) and the presence of two new bands at 3420 and 3340 cm^{-1} due to NH_2 and NH functional groups confirm the structure of (**2**). The 1H NMR spectrum of **2** displayed two broad singlets at δ 4.0 and 7.8 due to NH_2 and NH protons, which are D_2O exchangeable, confirming the formation of isoxazolyl amino thiazole (**2**). One of the styryl protons appeared as a



- 3a/4a : Ar = C₆H₅
 3b/4b : Ar = 4-CH₃C₆H₄
 3c/4c : Ar = 4-CH₃OC₆H₄,
 3d/4d : Ar = 4-ClC₆H₄
 3e/4e : Ar = 2-ClC₆H₄,
 3f/4f : Ar = 2,6-Cl₂C₆H₃
 3g/4g : Ar = 2,4-Cl₂C₆H₃,
 3h/4h : Ar = 4-NO₂C₆H₄

SCHEME 1

doublet at δ 6.8 ($J = 12$ Hz), whereas another styryl proton signal, when clubbed with aromatic proton signals and a thiazole ring proton signal, appeared as a complex multiplet between δ 7.2–7.6. The isoxazole methyl proton exhibited a sharp singlet at δ 2.2. The Schiff bases (**3a–h**) exhibited characteristic stretching vibrations between 1620–1660 cm^{-1} due to the C=N functional group, and the ^1H NMR spectrum of **3** displayed the newly formed azomethine proton signal at δ 7.8 as a singlet. The compounds (**4a–h**) exhibited prominent absorption bands between 1675–1695 and 1210–1240 cm^{-1} due to C=O and C–S functionalities, respectively, in their IR spectra, and showed two distinct singlets at δ 4.2 and 6.4 due to the newly formed 1,3-thiazolan-4-ones ring (CH₂ and CH) protons respectively, in their ^1H NMR spectra. Mass spectral data

and elemental analyses further confirm the structures of compounds (2), (3), and (4).

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. ^1H NMR spectra were recorded on Bruker AC 300 spectrometer in CDCl_3 and with TMS as 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.

N4-{3-Methyl-5-[(E)-2-phenyl-1-ethenyl]-4-isoxazolyl}-1,3-thiazole-2,4-diamine (2)

To a solution of N1-{3-methyl-5-[(E)-2-phenyl-1-ethenyl]-4-isoxazolyl-2-chloroacetamide (1) (0.01 mol) in ethanol (20 mL), thiourea (0.015 mol) was added, and the reaction mixture was refluxed for 5–8 h. After completion of the reaction, the reaction mixture was allowed to cool down and was later poured into ice-cold water. The isolated solid was filtered and washed with 2% NaHCO_3 solution (15 mL) and 12% brine solution (10 mL), and then dried over MgSO_4 . Evaporation of the solvent furnished the crude product, which was further purified by recrystallization from absolute ethanol. Colorless solid (absolute ethanol), yield 73%, mp 105–107°C, IR (KBr); 3420, 3340 cm^{-1} , ^1H NMR (300 MHz, CDCl_3) δ : 2.2 (s, 3H, CH_3), 4.0 (bs, 2H, NH_2 , D_2O exchangeable), 6.8 (d, 1H, $\text{CH}=\text{CH}$, $J = 12\text{Hz}$), 7.2–7.6 (m, 5H, Ar-H & 1H, $\text{CH}=\text{CH}$, & 1H, thiazole-H), 7.8 (bs, 1H, NH, D_2O exchangeable), MS: m/z 299 (M^+). Anal. Calcd. for $\text{C}_{15}\text{H}_{14}\text{N}_4\text{OS}$; C, 60.40; H, 4.69; N, 18.79; S, 10.73 Found: C, 60.42; H, 4.60; N, 18.72; S, 10.78%.

N4-{3-Methyl-5-[(E)-2-phenyl-1-ethenyl]-4-isoxazolyl}-N2-[(E)-1-arylmethylidene]-1,3-thiazole-2,4-diamines (3a–h)

A mixture of isoxazolylthiazole (2) (0.01 mol) and aromatic aldehyde (0.01 mol) was taken in ethanol, 4–5 drops of glacial acetic acid was added to it, and the contents were refluxed on a steam bath for 3–5 h. After the completion of the reaction (monitored by TLC), the solvent was removed under reduced pressure. The residue was dissolved in ethylacetate (15 mL) and washed with 10% NaHCO_3 solution (2×20 mL),

TABLE I Physical Data of Compounds (3a-h)*

Compd.	Mp (°C)	Yield (%)	Mol. Formula (Mol. Wt.)	Found (Calc.) %			
				C	H	N	S
3a	112	74	C ₂₂ H ₁₈ N ₄ OS (386)	68.30 (68.39)	4.69 (4.66)	14.42 (14.50)	8.22 (8.29)
3b	98	80	C ₂₃ H ₂₀ N ₄ OS (400)	69.02 (69.00)	4.95 (5.00)	14.08 (14.08)	8.09 (8.00)
3c	104	73	C ₂₃ H ₂₀ N ₄ O ₂ S (416)	66.37 (66.34)	4.72 (4.80)	14.08 (14.00)	7.66 (7.69)
3d	124	76	C ₂₂ H ₁₇ N ₄ OSCl (420)	62.79 (62.85)	4.11 (4.04)	13.38 (13.46)	7.65 (7.61)
3e	130	70	C ₂₂ H ₁₇ N ₄ OSCl (420)	62.78 (62.85)	4.09 (4.04)	13.36 (13.46)	7.59 (7.61)
3f	129	71	C ₂₂ H ₁₆ N ₄ OSCl ₂ (454)	58.20 (58.14)	3.45 (3.52)	12.39 (12.33)	7.09 (7.04)
3g	119	72	C ₂₂ H ₁₆ N ₄ OSCl ₂ (454)	58.18 (58.14)	3.49 (3.52)	12.35 (12.33)	7.07 (7.04)
3h	141	83	C ₂₂ H ₁₇ N ₅ O ₃ S (431)	61.29 (61.25)	3.88 (3.94)	16.19 (16.24)	7.48 (7.42)

*Compounds (3a-h) were purified by column chromatography.

TABLE II Physical Data of Compounds (4a-h)*

Compd.	Mp (°C)	Yield (%)	Mol. Formula (Mol. Wt.)	Found (Calc.) %			
				C	H	N	S
4a	123	76	C ₂₄ H ₂₀ N ₄ O ₂ S ₂ (460)	62.69 (62.60)	4.28 (4.34)	12.12 (12.17)	13.97 (13.91)
4b	113	82	C ₂₅ H ₂₂ N ₄ O ₂ S ₂ (474)	63.21 (63.29)	4.58 (4.64)	11.93 (11.81)	13.56 (13.50)
4c	129	80	C ₂₅ H ₂₂ N ₄ O ₃ S ₂ (490)	61.15 (61.22)	4.51 (4.48)	11.35 (11.42)	13.09 (13.06)
4d	132	78	C ₂₄ H ₁₉ N ₄ O ₂ S ₂ Cl (494)	58.34 (58.29)	3.73 (3.84)	11.30 (11.33)	12.88 (12.95)
4e	148	77	C ₂₄ H ₁₉ N ₄ O ₂ S ₂ Cl (494)	58.34 (58.29)	3.87 (3.84)	11.28 (11.33)	12.97 (12.95)
4f	138	75	C ₂₄ H ₁₈ N ₄ O ₂ S ₂ Cl ₂ (528)	54.61 (54.54)	3.32 (3.40)	10.52 (10.60)	12.19 (12.12)
4g	158	74	C ₂₄ H ₁₈ N ₄ O ₂ S ₂ Cl ₂ (528)	54.59 (54.54)	3.38 (3.40)	10.63 (10.60)	12.17 (12.12)
4h	162	85	C ₂₄ H ₁₉ N ₅ O ₃ S ₂ (505)	57.00 (57.02)	3.79 (3.76)	13.79 (13.86)	12.61 (12.67)

*Compounds (4a-h) were purified by column chromatography.

TABLE III Spectral Data of Compounds 3 and 4

Compd.	IR (ν_{\max} cm ⁻¹)	¹ H NMR (δ ppm)	Mass spectra m/z M ⁺
3a	3490, 1650	2.20 (s, 3H, CH ₃), 6.62 (d 1H, CH=CH, J = 12 Hz), 7.20–7.65 (m, 10H, Ar-H & 1H, thiazole-H & 1H, NH & 1H, CH=CH), 8.53 (s, 1H, CH=N)	386
3b	3370, 1635	2.15 (s, 3H, CH ₃), 2.40 (s, 3H, CH ₃), 6.76 (d, 1H, CH=CH, J = 12 Hz), 7.12–7.78 (m, 9H, Ar -H & 1H, thiazole-H & 1H, NH & 1H, CH=CH), 8.33 (s, 1H, CH=N)	400
3c	3390, 1645	2.30 (s, 3H, CH ₃), 3.72(s, 3H, OCH ₃), 6.80(d, 1H, CH=CH, J = 12 Hz), 7.21–7.85(m, 9H, Ar -H & 1H, thiazole-H & 1H, NH & 1H, CH=CH), 8.65(s, 1H, CH=N)	416
3d	3365, 1629	2.20 (s, 3H, CH ₃), 6.73 (d, 1H, CH=CH, J = 12 Hz), 7.12–7.65 (m, 9H, Ar-H & 1H, thiazole-H & 1H, NH & 1H, CH=CH), 8.60 (s, 1H, CH=N)	420
3e	3352, 1621	2.35 (s, 3H, CH ₃), 6.80 (d, 1H, CH=CH, J = 12 Hz), 7.05–7.65 (m, 9H, Ar-H & 1H, thiazole-H & 1H, NH & 1H, CH=CH), 8.65 (s, 1H, CH=N)	420
3f	3395, 1642	2.18 (s, 3H, CH ₃), 6.65 (d, 1H, CH=CH, J = 12 Hz), 7.08–7.69 (m, 8H, Ar-H & 1H, thiazole-H & 1H, NH & 1H, CH=CH), 8.55 (s, 1H, CH=N)	454
3g	3410, 1662	2.05 (s, 3H, CH ₃), 6.74 (d, 1H, CH=CH, J = 12 Hz), 7.12–7.64 (m, 8H, Ar-H & 1H, thiazole-H & 1H, NH & 1H, CH=CH), 8.80 (s, 1H, CH=N)	454
3h	3405, 1639	2.25 (s, 3H, CH ₃), 6.71 (d, 1H, CH=CH, J = 12 Hz), 7.13–7.82 (m, 9H, Ar-H & 1H, thiazole-H & 1H, NH & 1H, CH=CH), 8.86 (s, 1H, CH=N)	431
4a	3275, 1675, 1215	2.25 (s, 3H, CH ₃), 4.25 (s, 2H, CH ₂), 6.4 (s, 1H, CH), 7.25–8.26 (m, 10H, Ar -H & 2H, CH=CH, & 1H, thiazole - H), 8.62 (bs, 1H, NH, D ₂ O exchangeable)	460

(Continued on next page)

TABLE III Spectral Data of Compounds 3 and 4 (Continued)

Compd.	IR (ν_{max} cm^{-1})	^1H NMR (δ ppm)	Mass spectra m/z M^+
4b	3320, 1692, 1224	2.16 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 4.12 (s, 2H, CH_2), 6.33 (s, 1H, CH), 7.05–8.15 (m, 9H, Ar –H & 2H, $\text{CH}=\text{CH}$ & 1H, thiazole – H), 8.90 (bs, 1H, NH, D_2O exchangeable)	474
4c	3359, 1685, 1232	2.21 (s, 3H, CH_3), 3.82 (s, 3H, OCH_3), 4.22 (s, 2H, CH_2), 6.45 (s, 1H, CH), 7.10–7.93 (m, 9H, Ar –H & 2H, $\text{CH}=\text{CH}$ & 1H, thiazole – H), 8.92 (bs, 1H, NH, D_2O exchangeable)	490
4d	3371, 1679, 1245	2.25 (s, 3H, CH_3), 4.42 (s, 2H, CH_2), 6.15 (s, 1H, CH), 7.05–7.95 (m, 9H, Ar –H & 2H, $\text{CH}=\text{CH}$ & 1H, thiazole – H), 8.80 (bs, 1H, NH, D_2O exchangeable)	494
4e	3354, 1686, 1235	2.30 (s, 3H, CH_3), 4.32 (s, 2H, CH_2), 6.22 (s, 1H, CH), 6.92–8.05 (m, 9H, Ar –H & 2H, $\text{CH}=\text{CH}$ & 1H, thiazole – H), 8.90 (bs, 1H, NH, D_2O exchangeable)	494
4f	3320, 1690, 1210	2.25 (s, 3H, CH_3), 4.22 (s, 2H, CH_2), 6.45 (s, 1H, CH), 7.05–8.15 (m, 8H, Ar –H & 2H, $\text{CH}=\text{CH}$ & 1H, thiazole – H), 8.80 (bs, 1H, NH, D_2O exchangeable)	528
4g	3398, 1699, 1210	2.13 (s, 3H, CH_3), 4.12 (s, 2H, CH_2), 6.35 (s, 1H, CH), 7.12–8.26 (m, 8H, Ar –H & 2H, $\text{CH}=\text{CH}$ & 1H, thiazole – H), 8.85 (bs, 1H, NH, D_2O exchangeable)	528
4h	3325, 1682, 1227	2.05 (s, 3H, CH_3), 4.12 (s, 2H, CH_2), 6.35 (s, 1H, CH), 7.13–8.05 (m, 9H, Ar –H & 2H, $\text{CH}=\text{CH}$ & 1H, thiazole – H), 8.65 (bs, 1H, NH, D_2O exchangeable)	505

water (1×20 mL), and brine solution (1×20 mL). The organic layer was dried over anhydrous Na_2SO_4 . The crude compound was purified by column chromatography by elution with ethylacetate:n-hexane (1:9 ratio) (Table I).

3[4-(Methyl-5-[(E)-2-phenyl-1-ethenyl]-4-isoxazolyl)amino)-1,3-thiazol-2-yl]-2-aryl-1,3-thiazolan-4-ones (4a-h)

A mixture of compound (**3**) (0.01 mol) and mercaptoacetic acid (0.01 mol) was dissolved in 1,4-dioxane (15 mL), 0.2 g of anhydrous zinc chloride was added, and the contents were refluxed for 5–8 h. After completion of the reaction (monitored by TLC), the reaction mixture was allowed to cool down and was poured over crushed ice. The organic layer was extracted with ethyl acetate (20 mL); washed with 10% sodium bicarbonate solution (1 × 20 mL), water (2 × 20 mL), and 12% brine solution (1 × 20 mL); and dried over anhydrous sodium sulfate. The solvent was removed under vacuum, and the residue was recrystallized from benzene:hexane to give **4a-h** (Tables II and III).

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