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ISSN: 2231 – 3087(print)
ISSN: 2230 – 9632 (Online)
Coden HLEEAI
Vol. 4: (3), 2014, 381-389

SYNTHESIS OF ISOXAZOLYL QUINAZOLINES AND ISOXAZOLYL THIAZOLIDIN-4-ONES AS POSSIBLE BIODYNAMIC AGENTS

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Abstract

The synthesis of new isoxazolyl quinazolines **4** has been achieved upon the reaction of isoxazolyl 2-aminobenzamide **3** with aromatic aldehydes in the presence of PTSA. Isoxazolyl 4-thiazolidinones **6** have been obtained by condensation of isoxazolyl 2-aminobenzamide **3** with aromatic aldehydes in ethanol solvent, followed by cyclocondensation with mercapto acetic acid. Compounds **3-6** were characterized by IR, ^{1}H NMR and Mass spectral data.

Keywords: Isoxazolyl quinazolines , PTSA, cyclization, isoxazolyl thiazolidin-4-ones, cyclocondensation.

Introduction

The many and varied biological properties of quinazolines have engendered widespread interest in their synthesis[1, 2]. These compounds exhibit numerous pharmacological activites such as sedative, analgesic, diuretic, antihypertensive, antibiotic and antitumoral properties and many quinazolines have been demonstrated to inhibit kinases by competing with ATP for the kinases active site[3,4].

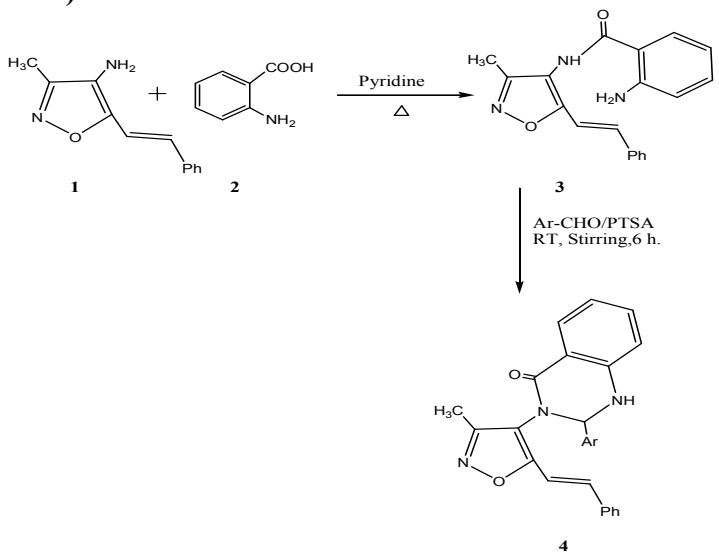
4-Thiazolidinones have gained unique importance due to broad spectrum of pharmacological activities which are reflected by their use as antitubercular,[5] antithyroid, [6] antimicrobial,[7] antiinflammatory,[8] analgesic,[9] anticonvulsant,[10] antiviral,[11] anticancer,[12] and antidiabetic[13] activities.

Isoxazole derivatives are reported with diverse structural features and versatile biological properties such as antitumor,[14] CNS–active,[15] muscle relaxant,[16] for the treatment of hyper cholsteremia and hyperlipidemia,[17] and as chemotherapeutic agents.[18]

Inspired by the biological profile of quinazolines, thiazolidinones and isoxazoles and their increasing importance in pharmaceutical and biological fields, and in connection with our research on the design and synthesis of biologically active and pharmacologically important new isoxazole substituted heterocycles, [19-22] it has been thought worth wile to synthesize isoxazolyl quinazolines and isoxazolyl thiazolidinones with a view to study their biological activity.

Results and Discussion

The reaction of 4-amino-3-methyl-5-styrylisoxazole **1** with anthranlic acid **2** in pyridine under reflux condition afforded (*E*)-2-amino-*N*-(3-methyl-5-styryl-4-isoxazolyl) benzamide **3** in good yield. Compound **3** on stirring with aromatic aldehydes in presence of *PTSA* at ambient temperature for 6 h, underwent cyclocondensation to furnish the corresponding 2-aryl-3 (3- methyl -5 - styryl-4-isoxazolyl) 4-oxo-1, 2, 3, 4 – tetrahydro quinazolines **4** in good yields **(Scheme- I).**



1 2 3 4

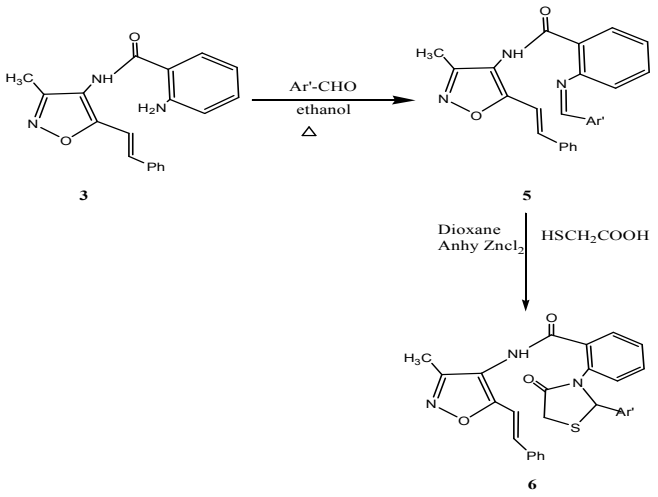
4, Ar	
a, C_6H_5	**e**, 4-$CH_3C_6H_5$
b, 2-ClC_6H_5	**f**, 4-$OCH_3C_6H_5$
c, 4-ClC_6H_5	**g**, 2-$CH_3C_6H_5$
d , 2-BrC_6H_5	**h**, 2-$OCH_3C_6H_5$

Scheme I

The IR spectrum of **3** displayed characteristic peaks at 3300, 3290, 3210 cm^{-1} due to CONH, and NH_2 functional groups, where as amide carbonyl appeared at 1680 cm^{-1}. ^1H NMR spectrum of **3** exhibited CONH and NH_2 proton signals at δ 8.62 and 8.88, which are D_2O exchangeable. The mass spectra of **3** showed molecular ion $[M+H]^+$ peak at *m/z* 320. The IR spectra of isoxazolyl quinazolines **4** exhibited characteristic absorption bands at 3250 and 1670 cm^{-1} due to NH and C=O functional groups respectively. ^1H NMR spectra of **4** displayed two prominent signals at δ 5.25 and 8.20 due to quinazoline ring CH and NH protons respectively. The mass spectrum of **4** showed a molecular ion $[M+H]^+$ peak at *m/z* 408 supporting the product formation.

(*E*)- 2- Amino – (3-methyl -5- styryl – 4- isoxazoly) benzamide **3** on condensation with aromatic aldehydes in boiling ethanol afforded the corresponding 2- [(*E*) - benzylidene amino]-*N*-(3-methyl - 5 - styryl- 4 - isoxazolyl) benzamides **5** in excellent yield. Cyclocondensation of mercapto acetic acid with **5** has been carried out in refluxing dioxane in presence of anhydrous $ZnCl_2$ for 6 h by using a Dean - stark apparatus.The reaction furnished the corresponding (*E*) –

N – [(3- methyl -5- styryl – 4- isoxazolyl) – 2- (4-oxo- 2-aryl thiazolidin-3-yl benzamides **6** in good yields **(Scheme II).**



5, **6** Ar'	
a, C_6H_5	**e**, 2-$CH_3C_6H_5$
b, 2-$NO_2C_6H_5$	**f**, 4-BrC_6H_5
c, 4-ClC_6H_5	**g**, 4-$CH_3C_6H_5$
d , 2,6 $Cl_2C_6H_5$	**h**, 4-$OCH_3C_6H_5$

Scheme II

The IR spectra of [(*E*) - benzylidene amino] - *N* – (3- methyl – 5- styryl - 4 – isoxazolyl) benzamides **5** manifested characteristic absoption peaks around 3230,1680 and 1625 cm^{-1} due to NH, CO and C=N functional group stretching vibrations respectively. The ^1H NMR spectra of **5** displayed a prominent singlet at δ 8.80 due to CH=N proton confirming Schiff base formation. The mass spectra of **5** very well agrees with the Schiff base structure by displaying the molecular ion $[M+H]^+$ peak at *m/z* 408. The IR spectra of (*E*) - *N* – [(3- methyl - 5 – styryl -4 –isoxazolyl] – 2 – (4 – oxo – 2 –aryl thiazolidin - 3 – yl) benzamides **6** exhibited characteristic absoption bands at 3235, 1680 and 1670 cm^{-1} due to NH, CO and thiazolidinone C=O functional groups respectively. ^1H NMR spectra of **6** shown two prominent singlets at δ 4.50 and 5.62 due to CONH and NCHAr protons respectively confirming cyclocondensation. The mass spectrum of **6** exhibited the molecular ion $[M+H]^+$ peak at *m/z* 482 supporting the thiazolidinone formaton.

In conclusion, a series of isoxazolyl quinazolines and isoxazolyl thiazolyl benzamides have been synthesized from readily available starting materials. These biheterocyclic system may be possible drug candidates based on the potential pharmacological activities of quinazoline, thiazolidinone and isoxazole nuclei. This synthesis benefits from a simple method of purification, not requiring chromatography, compliments this synthetic technology practical, easy to perform and facile. The biological activity of the compounds will be published elsewhere.

Experimental Section

Melting points are determined on a Cintex melting point apparatus and are uncorrected. The Purity of the compounds was checked by TLC. IR spectra was recorded in KBr on Perkin- Elmer spectrum BX series FT-IR spectrometer, ^{1}H NMR spectra on a Varian Gemini 300 MHz spectrometer using TMS as internal standard, and mass spectra on a Jeol JMC-300 spectrometer. C, H and N analysis were carried out on a Perkin-Elmer 240 analyzer.

Preparation of (*E*) - 2- amino - *N* - (3- methyl – 5 - styryl – 4 - isoxazolyl benzamide 3

To a solution of 4- amino 3- methyl- 5- styrylisoxazole **1** (0.01m mol) in pyridine (20 ml), anthranilic acid **2** (0.01 m mol), was added. The contents are refluxed for 8 h. After the completion of the reaction (monitored by TLC), the reaction mixture was allowed to cool. Then it is poured in to crushed ice, and solid that separated was filtered, washed with cold alcohol and recrystalized from ethanol. Yield 78%, m.p. 158-160^{0}C. IR(KBr) cm^{-1} 3300, 3290 (NH_2), 3210 (NH), 1680 (CO),1590 (C=C), 980 (C=C); ^{1}*H* NMR (300MHz,$CDCl_3$) δ ppm : 2.22 (s, 3H, CH3), 6.64 (d, 1H, CH = CH, *J* = 12Hz), 6.88 (d,1H, CH=CH, *J*=12 Hz), 7.01-7.79 (m, 9H, ArH), 8.62 (s, 1H, CONH, D_2O exchangeable), 8.88 (s, 2H, NH_2,D_2O exchangeable); MS: *m/z* 320 $[M+H]^+$. Anal.calcd for $C_{19}H_{17}N_3O_2$: C, 71.47; H, 5.32; N, 13.16. Found: C, 71.44; H, 5.35; N. 13.12%.

General procedure for the synthesis of 2 - aryl - 3 - (3 - methyl – 5- styryl - 4 - isoxazolyl) – 4 - oxo – 1, 2, 3, 4- tetrahydro quinazolines 4a-h

To a solution of isoxazolyl 2- amino benzamide **3** (0.01 mmol), in ethanol (20ml), *PTSA* (0.4g) and freshly distilled aromatic aldehyde 4 (0.01 m mol) was added and the mixture was stirred at room temperature for 6 h. After completion of the reaction (monitored by TLC), the reaction mixture was allowed to cool to room temperature. The separated solid was filtered to give crude product. Recrystalization from benzene afforded pure product.

2-Phenyl - 3 - (3- methyl -5 -styryl - 4 isoxazolyl) - 4 - oxo – 1, 2 ,3, 4 - tetrahydroquinazoline (4a)

Yield 80%, colourless solid. m.p. 175-177^{0}C. IR (KBr) cm^{-1}: 3250 (NH), 1670 (CO), 1595 (C=C), 980 (C=C).^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.25 (s, 3H, CH_3), 5.25 (s, 1H, NCHAr), 6.40 (d, 1H, CH=CH, *J*=12Hz), 6.65 (d, 1H, CH=CH, *J*=12Hz), 7.00 – 7.80 (m,14H, Ar-H), 8.20 (bs, 1H, NH, D_2O exchangeable); MS: *m/z* 408 $(M+H)^+$. Anal. Calcd for $C_{26}H_{21}N_3O_2$: C, 76.65; H, 5.15; N, 10.31. Found. C, 76.68; H, 5.13; N, 10.33%.

2- [2- Chlorophenyl – 3 - (3- methyl-5 - styryl - 4 isoxazolyl) - 4 - oxo - 1, 2, 3, 4 - tetrahydroquinazoline (4b)

Yield 78%, colourless solid. m.p. 189-191^{0}C. IR (KBr) cm^{-1}: 3200 (NH), 1675 (CO), 1590 (C=C), 980 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.20 (s, 6H, CH_3), 5.20 (s, 1H, NCHAr), 6.62 (d, 1H, CH=CH, *J*=12Hz), 6.75 (d, 1H, CH=CH, *J*=12Hz), 7.02 – 7.65 (m, 13H, Ar-H), 8. 10 (bs, 1H, NH, D_2O exchangeable); MS: *m/z* 442 $(M+H)^+$. Anal. Calcd for $C_{26}H_{20}N_3O_2Cl$: C, 70.74; H, 4.53; N, 9.52. Found. C, 70.72; H, 4.55; N, 9.50%.

2- [4- Chlorophenyl – 3 - (3- methyl- 5 - styryl - 4 isoxazolyl] - 4 - oxo - 1, 2, 3, 4 - tetrahydroquinazoline (4c)

Yield 76%, colourless solid. m.p. 199-201^{0}C. IR (KBr) cm^{-1}: 3210 (NH), 1670 (CO), 1575 (C=C), 975 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.25 (s, 3H, CH_3), 5.22 (s, 1H, NCHAr), 6.50 (d,1H, CH=CH, *J*=12Hz), 6.65 (d, 1H, CH=CH, *J*=12Hz), 6.95– 7.60 (m, 13H,

Ar-H), 8.25 (bs, 1H, NH, D_2O exchangeable); MS: *m/z* 442 $(M+H)^+$. Anal. Calcd for $C_{26}H_{20}N_3O_2Cl$: C, 70.74; H, 4.53; N, 9.52. Found. C, 70.70; H, 4.51; N, 9.55%.

2- [2- Bromophenyl– 3 - (3- methyl- 5 - styryl - 4 isoxazolyl] - 4 - oxo – 1, 2, 3, 4 - tetrahydroquinazoline (4d)

Yield 75%, colourless solid. m.p. 211-212^{0}C. IR (KBr) cm^{-1}: 3235 (NH), 1670 (CO), 1580 (C=C), 975 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.21 (s, 3H, CH_3), 5.28 (s, 1H, NCHAr) 6.62 (d, 1H, CH=CH, *J* =12Hz), 6.70 (d, 1H, CH=CH, *J* =12Hz), 6.90– 7.62 (m, 13H, Ar-H), 8.22 (bs, 1H, NH, D_2O exchangeable); MS: *m/z* 486 $(M+H)^+$. Anal. Calcd for $C_{26}H_{20}N_3O_2Br$: C, 64.32; H, 4.12; N, 8.65. Found. C, 64.35; H, 4.10; N, 8.68%.

2- [4- Methylphenyl– 3 - (3- methyl- 5 - styryl - 4 isoxazolyl] - 4 - oxo – 1, 2, 3, 4 - tetrahydroquinazoline (4e)

Yield 80%, colourless solid. m.p. 170-172^{0}C. IR (KBr) cm^{-1}: 3200 (NH), 1675 (CO), 1600 (C=C), 980 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.20 (s, 3H, isoxazole-CH_3), 2.45 (s, 3H, Ar-CH_3), 5.25 (s, 1H, NCHAr) 6.60 (d, 1H, CH=CH, *J* =12Hz), 6.75 (d, 1H, CH=CH, *J* =12Hz), 7.00– 7.50 (m, 13H, Ar-H), 8.21 (bs, 1H, NH, D_2O exchangeable); MS: *m/z* 422 $(M+H)^+$. Anal. Calcd for $C_{27}H_{23}N_3O_2$: C, 76.95; H, 5.46; N, 9.97. Found. C, 76.98; H, 5.44; N, 9.94%.

2- [4- Methoxyphenyl– 3 - (3- methyl- 5 - styryl - 4 isoxazolyl] - 4 - oxo – 1, 2, 3, 4 - tetrahydroquinazoline (4f)

Yield 80%, colourless solid. m.p. 182-184^{0}C. IR (KBr) cm^{-1}: 3210 (NH), 1670 (CO), 1590 (C=C), 975 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.25 (s, 3H, isoxazole-CH_3), 3.75 (s, 3H, OCH_3), 5.27 (s, 1H, NCHAr) 6.50 (d, 1H, CH=CH, *J* =12Hz), 6.65 (d, 1H, CH=CH, *J* =12Hz), 6.90– 7.50 (m, 13H, Ar-H), 8.10 (bs, 1H, NH, D_2O exchangeable); MS: *m/z* 438 $(M+H)^+$. Anal. Calcd for $C_{27}H_{23}N_3O_3$: C, 74.14; H, 5.26; N, 9.61. Found. C, 74.19; H, 5.22; N, 9.60%.

2- [2- Methylphenyl– 3 - (3- methyl- 5 - styryl - 4 isoxazolyl] - 4 - oxo – 1, 2, 3, 4 - tetrahydroquinazoline (4g)

Yield 80%, colourless solid. m.p. 181-183^{0}C. IR (KBr) cm^{-1}: 3200 (NH), 1680 (CO), 1600 (C=C), 980 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.25 (s, 3H, isoxazole-CH_3), 2.40 (s, 3H, Ar-CH_3), 5.25 (s, 1H, NCHAr) 6.62 (d, 1H, CH=CH, *J* =12Hz), 6.80 (d, 1H, CH=CH, *J* =12Hz), 7.00– 7.72 (m, 13H, Ar-H), 8.25 (bs, 1H, NH, D_2O exchangeable); MS: *m/z* 422 $(M+H)^+$. Anal. Calcd for $C_{27}H_{23}N_3O_2$: C, 76.95; H, 5.46; N, 9.97. Found. C, 76.91; H, 5.49; N, 9.95%.

2- [2- Methoxyphenyl– 3 - (3- methyl- 5 - styryl - 4 isoxazolyl] - 4 - oxo – 1, 2, 3, 4 - tetrahydroquinazoline (4h)

Yield 78%, colourless solid. m.p. 165-167^{0}C. IR (KBr) cm^{-1}: 3210 (NH), 1670 (CO), 1595 (C=C), 980 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.22 (s, 3H, isoxazole-CH_3), 3.80 (s, 3H, OCH_3), 5.20 (s, 1H, NCHAr) 6.65 (d, 1H, CH=CH, *J* =12Hz), 6.78 (d, 1H, CH=CH, *J*=12Hz), 7.00– 7.65 (m, 13H, Ar-H), 8.20 (bs, 1H, NH, D_2O exchangeable); MS: *m/z* 438 $(M+H)^+$. Anal. Calcd for $C_{27}H_{23}N_3O_3$: C, 74.14; H, 5.26; N, 9.61. Found. C, 74.11; H, 5.23; N, 9.64%.

General procedure for the preparation of 2 – [(*E*) –benzylideneamino]- *N*- (3- methyl – 5- styryl- 4- isoxazolyl) benzamides (5a-h)

(*E*)- 2- Amino- *N*- (3-methyl- 5 – styryl – 4 isoxazolyl benzamide **3** (1 m mol) and freshly distilled aromatic aldehyde (1 m mol) were refiuxed in ethanol for 1 h. After the completion of

the reaction (monitored by TLC), the reaction mixture is allowed to cool to room temperature. The precipitate that formed was filtered off, washed with cold alcohol, and recrystalized from ethanol.

2 – [(*E*) –Benzylideneamino]- *N*- (3- methyl – 5- styryl- 4- isoxazolyl) benzamide (5a)

Yield 85%, colourless solid. m.p. 168-170^{0}C. IR (KBr) cm^{-1}: 3230 (NH), 1680 (CO), 1625 (C=N), 1590 (C=C), 980 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.20 (s, 3H, isoxazole-CH_3), 6.62 (d, 1H, CH=CH, *J* =12Hz), 6.80 (d, 1H, CH=CH, *J* =12Hz), 6.95– 7.50 (m, 14H, Ar-H), 8.66 (bs, 1H, CONH, D_2O exchangeable) 8.80 (s, 1H, CH=N); MS: *m/z* 408 $(M+H)^+$. Anal. Calcd for $C_{26}H_{21}N_3O_2$: C, 76.65; H, 5.15; N, 10.31. Found. C, 76.62; H, 5.11; N, 10.35%.

2 - [(*E*) - 2- Nitrobenzylideneamino]- *N*- (3- methyl – 5- styryl- 4- isoxazolyl) benzamide (5b)

Yield 80%, colourless solid. m.p. 180-182^{0}C. IR (KBr) cm^{-1}: 3210 (NH), 1675 (CO), 1625 (C=N), 1560 (C=C) and 1325 (NO_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.25 (s, 3H, isoxazole-CH_3), 6.60 (d, 1H, CH=CH, *J* =12Hz), 6.75 (d, 1H, CH=CH, *J* =12Hz), 7.00– 7.80 (m, 13H, Ar-H), 8.50 (bs, 1H, CONH, D_2O exchangeable) 8.65 (s, 1H, CH=N); MS: *m/z* 453 $(M+H)^+$. Anal. Calcd for $C_{26}H_{20}N_4O_4$: C, 69.02; H, 4.42; N, 12.38. Found. C, 69.06; H, 4.40; N, 12.35%.

2 – [(*E*)- 4- Chlorobenzylideneamino]- *N*- (3- methyl – 5- styryl- 4- isoxazolyl) benzamide (5c)

Yield 82%, colourless solid. m.p. 185-187^{0}C. IR (KBr) cm^{-1}: 3235 (NH), 1670 (CO), 1640 (C=N), 1590 (C=C), 980 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.25 (s, 3H, isoxazole-CH_3), 6.60 (d, 1H, CH=CH, *J* =12Hz), 6.82 (d, 1H, CH=CH, *J* =12Hz), 7.00– 7.77 (m, 13H, Ar-H), 8.52 (bs,1H, CONH, D_2O exchangeable) 8.69 (s, 1H, CH=N); MS: *m/z* 442 $(M+H)^+$. Anal. Calcd for $C_{26}H_{20}N_3O_2Cl$: C, 70.74; H, 4.53; N, 9.52. Found. C, 70.77; H, 4.55; N, 9.49%.

2 – [(*E*)- 2,6-Dichlorobenzylideneamino]- *N*- (3- methyl – 5- styryl- 4- isoxazolyl) benzamide (5d)

Yield 82%, colourless solid. m.p. 200-202^{0}C. IR (KBr) cm^{-1}: 3230 (NH), 1680 (CO), 1645 (C=N), 1560 (C=C), 980 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.22 (s, 3H, isoxazole-CH_3), 6.55 (d, 1H, CH=CH, *J* =12Hz), 6.70 (d, 1H, CH=CH, *J* =12Hz), 6.90– 7.50 (m, 13H, Ar-H), 8.33 (bs,1H, CONH, D_2O exchangeable) 8.60 (s, 1H, CH=N); MS: *m/z* 476$(M+H)^+$. Anal. Calcd for $C_{26}H_{19}N_3O_2Cl_2$: C, 65.68; H, 4.00; N, 8.84. Found. C, 65.70; H, 4.02; N, 8.88%.

2 – [(*E*)- 2- Methylbenzylideneamino]- *N*- (3- methyl – 5- styryl- 4- isoxazolyl) benzamide (5e)

Yield 85%, colourless solid. m.p. 172-174^{0}C. IR (KBr) cm^{-1}: 3233 (NH), 1675 (CO), 1640 (C=N), 1555 (C=C), 975 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.27 (s, 3H, isoxazole-CH_3), 2.40 (s, 3H, Ar CH_3), 6.62 (d, 1H, CH=CH, *J* =12Hz), 6.80 (d, 1H, CH=CH, *J* =12Hz), 7.00– 7.90 (m, 13H, Ar-H), 8.60 (bs,1H, CONH, D_2O exchangeable) 8.82 (s, 1H, CH=N); MS: *m/z* 422 $(M+H)^+$. Anal. Calcd for $C_{27}H_{23}N_3O_2$: C, 76.95; H, 5.46; N, 9.97. Found. C, 76.91; H, 5.48; N, 10.00%.

2 – [(*E*)- 4- Bromobenzylideneamino]- *N*- (3- methyl – 5- styryl- 4- isoxazolyl) benzamide (5f)

Yield 80%, colourless solid. m.p. 192-194^{0}C. IR (KBr) cm^{-1}: 3235 (NH), 1670 (CO), 1645 (C=N), 1550 (C=C), 980 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.25 (s, 3H, isoxazole-CH_3), 6.55 (d, 1H, CH=CH, *J* =12Hz), 6.72 (d, 1H, CH=CH, *J* =12Hz), 6.90– 7.62(m, 13H, Ar-H), 8.32 (bs,1H, CONH, D_2O exchangeable) 8.55 (s, 1H, CH=N); MS: *m/z* 486 $(M+H)^+$. Anal. Calcd for $C_{26}H_{20}N_3O_2Br$: C, 64.32; H, 4.12; N, 8.65. Found. C, 64.30; H, 4.15; N, 8.61%.

2 – [(*E*)- 4- Methylbenzylideneamino]- *N*- (3- methyl – 5- styryl- 4- isoxazolyl) benzamide (5g)

Yield 85%, colourless solid. m.p. 175-177^{0}C. IR (KBr) cm^{-1}: 3230 (NH), 1670 (CO), 1645 (C=N), 1555 (C=C), 975 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.25 (s, 3H, isoxazole-CH_3), 2.47 (s, 3H, Ar CH_3), 6.61 (d, 1H, CH=CH, *J* =12Hz), 6.69 (d, 1H, CH=CH, *J* =12Hz), 7.00– 7.66 (m, 13H, Ar-H), 8.22 (bs,1H, CONH, D_2O exchangeable) 8.59 (s, 1H, CH=N); MS: *m/z* 422 $(M+H)^+$. Anal. Calcd for $C_{27}H_{23}N_3O_2$: C, 76.95; H, 5.46; N, 9.97. Found. C, 77.00; H, 5.49; N, 9.95%.

2 – [(*E*)- 4- Methoxybenzylideneamino]- *N*- (3- methyl – 5- styryl- 4- isoxazolyl) benzamide (5h)

Yield 82%, colourless solid. m.p. 182-184^{0}C. IR (KBr) cm^{-1}: 3240 (NH), 1670 (CO), 1635 (C=N), 1560 (C=C), 975 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.20 (s, 3H, isoxazole-CH_3), 3.80 (s, 3H, OCH_3), 6.60 (d, 1H, CH=CH, *J* =12Hz), 6.75 (d, 1H, CH=CH, *J* =12Hz), 6.90– 7.50 (m, 13H, Ar-H), 8.50 (bs,1H, CONH, D_2O exchangeable) 8.68 (s, 1H, CH=N); MS: *m/z* 438 $(M+H)^+$. Anal. Calcd for $C_{27}H_{23}N_3O_3$: C, 74.14; H, 5.26; N, 9.61. Found. C, 74.11; H, 5.29; N, 9.63%.

General procedure for the synthesis of (*E*)- *N* - (3 - methyl – 5- styryl- 4- isoxazolyl) -2- (4-oxo-2-aryl thiazolidin-3-yl) benzamides (6a-h)

2 – [(*E*) –Benzylideneamino]- *N*- (3- methyl – 5- styryl- 4- isoxazolyl) benzamide **5** (0.01m mol), and mercapto acetic acid (0.01 m mol) were refluxed in dioxane (15 ml) in presence of traces of anhydrous $ZnCl_2$ using Dean- Stark apparatus for 6 h. After completion of the reaction (monitored by TLC), the reaction mixture was cooled, and poured in to ice - cold water. The separated solid was filtered, and recrystallized from ethanol.

(*E*)- *N* - (3 - Methyl – 5- styryl- 4- isoxazolyl) -2- (4-oxo-2-phenyl-thiazolidin-3-yl) benzamide (6a)

Yield 80%, colourless solid. m.p. 195-197^{0}C. IR (KBr) cm^{-1}: 3235 (NH), 1680 (CO), 1670 (CO), 1590 (C=C), 980 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.22 (s, 3H, isoxazole-CH_3), 4.50 (s, 2H, CH_2), 5.62 (s, 1H, NCHAr), 6.60 (d, 1H, CH=CH, *J* =12Hz), 6.85 (d, 1H, CH=CH, *J* =12Hz), 7.00– 7.10 (m, 14H, Ar-H), 8.65 (bs,1H, CONH, D_2O exchangeable); MS: *m/z* 482 $(M+H)^+$. Anal. Calcd for $C_{28}H_{23}N_3O_3S$: C, 69.85; H, 4.78; N, 8.73. Found. C, 69.88; H, 4.82; N, 8.70%.

(*E*)- *N* - (3 - Methyl – 5- styryl- 4- isoxazolyl) -2- (4-oxo-2-(2-nitro phenyl-thiazolidin-3-yl) benzamide (6b)

Yield 80%, colourless solid. m.p. 202-204^{0}C. IR (KBr) cm^{-1}: 3233 (NH), 1685 (CO), 1670 (CO), 1585 (C=C), 975 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.20 (s, 3H, isoxazole-CH_3), 4.48 (s, 2H, CH_2), 5.60 (s, 1H, NCHAr), 6.55 (d, 1H, CH=CH, *J* =12Hz), 6.70 (d, 1H, CH=CH, *J* =12Hz), 6.90– 7.50 (m, 13H, Ar-H), 8.50 (bs,1H, CONH, D_2O exchangeable); MS: *m/z* 527 $(M+H)^+$. Anal. Calcd for $C_{28}H_{22}N_4O_5S$: C, 63.87; H, 4.18; N, 10.64. Found. C, 63.85; H, 4.15; N, 10.66%.

(*E*)- *N* - (3 - Methyl – 5- styryl- 4- isoxazolyl) -2- (4-oxo-2-(4-chloro phenyl-thiazolidin-3-yl) benzamide (6c)

Yield 78%, colourless solid. m.p. 215-217^{0}C. IR (KBr) cm^{-1}: 3230 (NH), 1670 (CO), 1660 (CO), 1545 (C=C), 980 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.25 (s, 3H, isoxazole-CH_3), 4.55 (s, 2H, CH_2), 5.58 (s, 1H, NCHAr), 6.65 (d, 1H, CH=CH, *J* =12Hz), 6.80 (d, 1H, CH=CH,

J =12Hz), 7.00– 7.70 (m, 13H, Ar-H), 8.66 (bs,1H, CONH, D_2O exchangeable); MS: *m/z* 516 $(M+H)^+$. Anal. Calcd for $C_{28}H_{22}N_3O_3SCl$: C, 65.24; H, 4.27; N, 8.15. Found. C, 65.22; H, 4.25; N, 8.18%.

(*E*)- *N* - (3 - Methyl – 5- styryl- 4- isoxazolyl) -2- (4-oxo-2-(2,6-dichloro phenyl-thiazolidin-3-yl) benzamide (6d)

Yield 75%, colourless solid. m.p. 220-222^{0}C. IR (KBr) cm^{-1}: 3235 (NH), 1680 (CO), 1665 (CO), 1585 (C=C), 975 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.20 (s, 3H, isoxazole-CH_3), 4.42 (s, 2H, CH_2), 5.37 (s, 1H, NCHAr), 6.52 (d, 1H, CH=CH, *J* =12Hz), 6.75 (d, 1H, CH=CH, *J* =12Hz), 6.90– 7.50 (m, 13H, Ar-H), 8.66 (bs,1H, CONH, D_2O exchangeable); MS: *m/z* 550 $(M+H)^+$. Anal. Calcd for $C_{28}H_{21}N_3O_3SCl_2$: C, 61.20; H, 3.82; N, 7.65. Found. C, 61.25; H, 3.87; N, 7.66%.

(*E*)- *N* - (3 - Methyl – 5- styryl- 4- isoxazolyl) -2- (4-oxo-2-(2-methyl phenyl-thiazolidin-3-yl) benzamide (6e)

Yield 82%, colourless solid. m.p. 208-210^{0}C. IR (KBr) cm^{-1}: 3200 (NH), 1675 (CO), 1665 (CO), 1580 (C=C), 980 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.20 (s, 3H, isoxazole-CH_3), 2.28 (s, 3H, Ar-CH_3), 4.48 (s, 2H, CH_2), 5.90 (s, 1H, NCHAr), 6.60 (d, 1H, CH=CH, *J* =12Hz), 6.75 (d, 1H, CH=CH, *J* =12Hz), 6.95– 7.60 (m, 13H, Ar-H), 8.50 (bs,1H, CONH, D_2O exchangeable); MS: *m/z* 496 $(M+H)^+$. Anal. Calcd for $C_{29}H_{25}N_3O_3S$: C, 70.30; H, 5.05; N, 8.48. Found. C, 70.32; H, 5.00; N, 8.45%.

(*E*)- *N* - (3 - Methyl – 5- styryl- 4- isoxazolyl) -2- (4-oxo-2-(4-Bromo phenyl-thiazolidin-3-yl) benzamide (6f)

Yield 80%, colourless solid. m.p. 228-230^{0}C. IR (KBr) cm^{-1}: 3210 (NH), 1680 (CO), 1670 (CO), 1560 (C=C), 975 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.25 (s, 3H, isoxazole-CH_3), 4.32 (s, 2H, CH_2), 5.51 (s, 1H, NCHAr), 6.66 (d, 1H, CH=CH, *J* =12Hz), 6.83 (d, 1H, CH=CH, *J* =12Hz), 7.00– 7.79 (m, 13H, Ar-H), 8.23 (bs,1H, CONH, D_2O exchangeable); MS: *m/z* 560 $(M+H)^+$. Anal. Calcd for $C_{28}H_{22}N_3O_3SBr$: C, 60.10; H, 3.93; N, 7.51. Found. C, 60.05; H, 3.97; N, 7.55%.

(*E*)- *N* - (3 - Methyl – 5- styryl- 4- isoxazolyl) -2- (4-oxo-2-(4-methyl phenyl-thiazolidin-3-yl) benzamide (6g)

Yield 82%, colourless solid. m.p. 190-192^{0}C. IR (KBr) cm^{-1}: 3225 (NH), 1670 (CO), 1665 (CO), 1570 (C=C), 980 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.22 (s, 3H, isoxazole-CH_3), 2.40 (s, 3H, Ar-CH_3), 4.36 (s, 2H, CH_2), 5.48 (s, 1H, NCHAr), 6.62(d, 1H, CH=CH, *J* =12Hz), 6.78 (d, 1H, CH=CH, *J* =12Hz), 6.95– 7.60 (m, 13H, Ar-H), 8.55 (bs,1H, CONH, D_2O exchangeable); MS: *m/z* 496 $(M+H)^+$. Anal. Calcd for $C_{29}H_{25}N_3O_3S$: C, 70.30; H, 5.05; N, 8.48. Found. C, 70.35; H, 5.08; N, 8.52%.

(*E*)- *N* - (3 - Methyl – 5- styryl- 4- isoxazolyl) -2- (4-oxo-2-(4-methoxy phenyl-thiazolidin-3-yl) benzamide (6h)

Yield 85%, colourless solid. m.p. 218-220^{0}C. IR (KBr) cm^{-1}: 3210 (NH), 1680 (CO), 1670 (CO), 1565 (C=C), 975 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.25 (s, 3H, isoxazole-CH_3), 3.75 (s, 3H, O-CH_3), 4.50 (s, 2H, CH_2), 5.58 (s, 1H, NCHAr), 6.65 (d, 1H, CH=CH, *J* =12Hz), 6.77 (d, 1H, CH=CH, *J* =12Hz), 7.00 – 8.00 (m, 13H, Ar-H), 8.55 (bs,1H, CONH, D_2O exchangeable); MS: *m/z* 512 $(M+H)^+$. Anal. Calcd for $C_{29}H_{25}N_3O_4S$: C, 68.10; H, 4.89; N, 8.25. Found. C, 68.06; H, 4.92; N, 8.25%.

Acknowledgements

The authors are thankful to the Head, Department of Chemistry, Kakatiya University, Warangal for facilities and to the Director, Indian Institute of Chemical Technology, Hyderabad for recording ^{1}H NMR and Mass Spectra.

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