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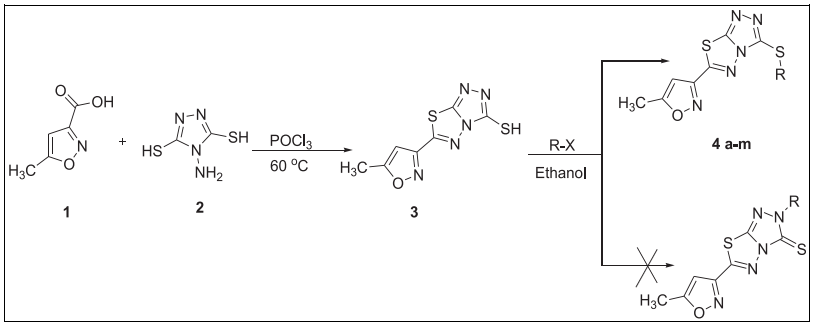
Received August 23, 2013
DOI 10.1002/jhet.2168
Published online 7 October 2014 in Wiley Online Library (wileyonlinelibrary.com).




A new series of isoxazole substituted fused triazolo-thiadiazoles have been synthesized by the cyclocondensation of 5-methylisoxazole-3-craboxylic acid and 4-amino 1,2-4-triazole- 3,5-dithiol using phosphorous oxychloride. The cyclised intermediate 6-(5-methylisoxazol-3-yl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole-3-thiol later on S-alkylated with different alkyl halides in ethanol to give the title products in good to excellent yields.

*J. Heterocyclic Chem.*, **52**, 1614 (2015).

## INTRODUCTION

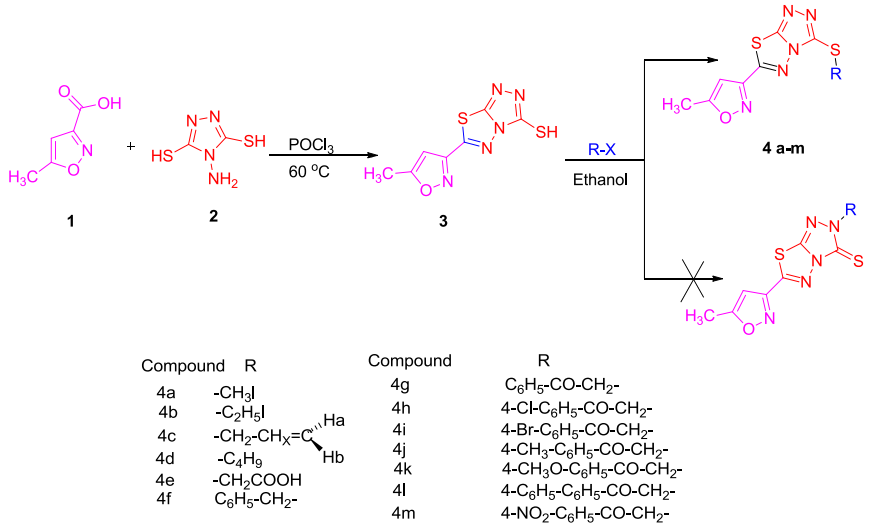
Heterocyclic compounds having nitrogen atom have received much attention as pharmacological probes. Isoxazole is one of the five member heterocyclic compound having promising biological significance. Isoxazole and their derivatives have been extensively used as important pharmacophore in drug molecules. Isoxazole moiety is having broad spectrum of pharmacological activities such as antibacterial [1,2], antiviral [3], anti-parasitic [4], antitumor [5], anti-tuberculosis [6,7], and anti-inflammatory [8].

In recent years, fused 1,2,4-triazolo[3,4-b] 1,3,4-thiadiazoles have significant attraction due to their promising pharmacological activities such as anti-microbial [9,10], anti-inflammatory [11,12], antitumor [13–15], anti oxidant [16], analgesic [17], antiviral [18,19], antifungal [20], antibacterial [21], anti-helminthes [22], CNS stimulants [23], and plant growth regulatory effects [24]. Prompted by the aforementioned biological significance of isoxazoles and triazolo-thiadiazole derivatives, it is desired to synthesize the isoxazole substituted triazolo-thiadiazole derivatives (Scheme 1).

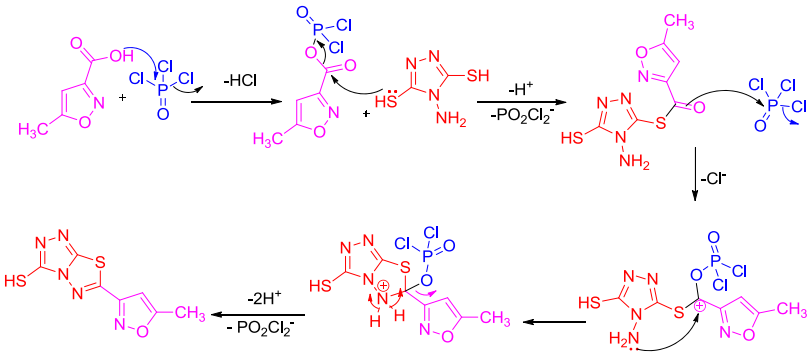
## RESULTS AND DISCUSSION

The starting material 4-amino 1,2,4-triazole 3,5-dithiol was prepared according to the literature procedure [25]. 4-Amino 1,2,4-triazole-3,5-dithiol undergoes cyclocondensation with 5-methylisoxazole-3-carboxylic acid by the involvement of thiol and amino functionalities of 4-amino 1,2,4-triazole-3,5-dithiol in phosphorous oxychloride. The key step of the cyclocondensation is the formation of phosphate ester followed by the removal of $OPOCl_2$ as anion. The compound 3 on reaction with various alkyl halides provided the cyclized products **4** (Scheme 2). This is a regioselective S-alkylation. The alkylation of **3** with alkyl halides may result in different types of products, such as N-alkylated, S-alkylated, or a mixture of both. In the present investigation, a mixture of products is not formed (as evidenced by TLC). The formation of S-alkylated products in preference to N-alkylated products can be explained as due to high nucleophilicity of thiol group. The formation of S-alkylated products was confirmed by spectral data. All the synthesized compounds were characterized by their physical, analytical, and spectral data. The intermediate 6-(5-methylisoxazol-3-yl)-[1,2,4]triazolo [3,4-b][1,3,4]thiadiazole-3-thiol (**3**) in $^1$H-NMR spectrum showed a peak at 14.37 δ ppm, which corresponds to the thiol functional group that disappeared in the next step confirming the S-alkylation. The IR spectrum of the compound **4i** showed characteristic bands at 1679, 1586, 1257,1193 $cm^{-1}$ due to carbonyl (–C═O), C═N, C–O–N, and C–S stretching vibrational frequencies, respectively. The $^1$H-NMR spectrum of 2-(6-(5-methylisoxazol-3-yl)-[1,2,4]triazolo[3,4-b] [1,3,4]thiadiazol-3-ylthio)-1-(4-bromophenyl) ethanone (**4i**) showed three singlet peaks at 2.55, 4.98, and 6.89 δ ppm due to $CH_3$, S–$CH_2$ and Isoxazole-C-4 proton, respectively. Two doublets at 7.77 and 7.94 δ ppm are due to aromatic protons. The $^{13}$C-NMR spectrum of compound **4i** showed characteristic peaks at 11.92, 127.99–134.03,173.08,

**Scheme 1.** Synthesis of 6-(5-Methyl-isoxzol-3yl)-3-alkyl sulfanyl-[1,2,4]triazolo- [3,4b][1,3,4]thiadiazole.




**Scheme 2.** Plausible mechanism.




and 192.52 δ ppm are due to $CH_3$, C=C, =C–O, –C=O carbons, respectively.

## CONCLUSION

In brief, we have synthesized the thioalkyl-substituted nitrogen-bridged triazolo-thiadiazoles via cyclocondensation followed by alkylation in good to excellent yields.

## EXPERIMENTAL

**General.** The general synthetic procedure for the compound **4** was described in the succeeding text. All the reagents and chemicals used were purchased from commercial sources and used without further purification unless otherwise mentioned. The progress of all the reactions was monitored with TLC by using silica gel plates (E. Merck, Darmstadt, Germany) and visualization was done by exposure to Ultra-Violet light and Iodine-chamber. Melting points were determined on open capillaries with the Stuart Melting Point apparatus (Stuart, Staffordshire, UK; SMP-30). Infrared spectrum was run on Perkin Elmer (Spectrum-100S, Perkin-Elmer, Walthan, MA) spectrometer. The $^1$H-NMR spectra and $^{13}$C-NMR spectra were recorded on Bruker WM-400 spectrometer (Bruker, Falladan, Switzerland) at 400 and 100 MHz in δ ppm by using DMSO-$d_6$ as a solvent and TMS as an internal standard. The Mass spectrum was acquired on Water Micromass Quattro API technique in positive or negative modes. Elemental analysis was determined by using Carlo Erba 1108 instrument.

**Synthesis of 6-(5-Methylisoxazol-3-yl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole-3-thiol. (3).** A mixture of 5-methylisoxazole-3-carboxylic acid (10 mmol) and 4-amino-4H-[1,2,4]triazole-3,5-dithiol (10 mmol) was taken in a round bottom flask containing phosphorous oxy chloride (15 mL). The mixture was stirred at room temperature for 30 min then heated at 60°C for about 5 h. After completion of the reaction (monitored with TLC), the reaction mixture was cooled to room temperature and gradually poured into crushed ice with stirring. Then it was neutralized by using 5% sodium bicarbonate solution. The white solid separated was filtered, washed thoroughly with cold water, and recrystallized from methanol. Yield (78%); mp 292–294°C; IR (KBr, $cm^{-1}$) 1593 (C=N); 1263 (C–O–N); 2880 (S–C); $^1$H-NMR (DMSO-$d_6$, δ ppm): 2.56 (3H, S, $CH_3$), 7.03 (1H, S, Ar–H), 14.37 (1H, S, S–H).

**General procedure for the synthesis of 6-(5-Methyl-Isoxzol-3yl)-3-alkyl sulfanyl-[1,2,4]triazolo-[3,4-b][1,3,4]thiadiazole: (4a–m).** 6-(5-Methylisoxazol-3-yl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole-3-thiol (**3**) (1 mmol) was dissolved in ethanol (5 mL) then

alkyl halide (1 mmol) was added and refluxed for 4–6 h. After completion of the reaction (monitored with TLC), the reaction mixture was allowed to cool to room temperature. The separated solid was filtered. The compound so obtained was recrystallized from suitable solvent.

***6-(5-Methylisoxazol-3-yl)-3-(methylthio)-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazole (4a).*** Yield (79%); mp 220–222°C; IR (KBr, $cm^{-1}$) 1599 (C═N); 1255 (C–O–N); 1191 (S–C); $^1$H-NMR (DMSO-$d_6$, δ ppm): 2.57 (3H, S, $CH_3$), 2.81 (3H, S,-S–$CH_3$), 6.64 (1H, S, Ar–H). $^{13}$C-NMR (DMSO-$d_6$, δ ppm): 11.87; 14.76; 100.05; 143.31; 153.71; 155.27; 156.71; 173.05; *Anal*. Calcd for $C_8H_7N_5OS_2$: C, 37.93; H, 2.79; N, 27.65; S, 25.32. Found: C, 37.87; H, 2.83; N, 27.70; S, 25.27; MS (ES *m/z*): 275.95 $[M+Na]^+$ 100%; 253.95 $[M+1]^+$.

***3-(Ethylthio)-6-(5-methylisoxazol-3-yl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole (4b).*** Yield: (82%); mp 174–176°C; IR (KBr $cm^{-1}$) 1598 (C═N); 1262 (C–O–N); 1153 (S–C); $^1$H-NMR (DMSO-$d_6$; δ ppm): 1.34 (t, $J=7.6$ Hz, 3H, $CH_3$); 2.55 (3H, S, $CH_3$);3.24 (q, $J=7.2$ Hz, 2H, $CH_2$ ); 7.02 (S, 1H, Ar–H); $^{13}$C-NMR (DMSO-$d_6$, δ ppm): 11.88; 15.07; 27.12; 100.05; 142.18; 153.82; 155.28; 156.79; 173.05; *Anal*. Calcd for $C_9H_9N_5OS_2$: C, 40.44; H, 3.39; N, 26.20; S, 23.99. Found: C, 40.49; H, 3.34; N, 26.26; S, 23.93; MS (ES *m/z*): 289.95 $[M+Na]^+$ 100%; 267.93 $[M+1]^+$.

***3-(Allylthio)-6-(5-methylisoxazol-3-yl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole (4c).*** Yield (78%); mp 130.5-131.7°C; IR (KBr $cm^{-1}$) 1591(C═N); 1254 (C–O–N); 1151 (S–C); $^1$H-NMR (DMSO-$d_6$; δ ppm): 2.57 ( S, 3H, $CH_3$); 3.92 (d, $J=7.2$ Hz, 2H; S–$CH_2$); 5.13 (d, $J$ $H_x$, $H_A=10$ Hz, 1H, $H_A$); 5.25 (d, $J$ $H_x$, $H_B=17.2$ Hz, 1H, $H_B$); 5.94–6.03 (m, 1H, $H_X$); 6.66 (s, 1H, Ar–H); *Anal*. Calcd for $C_{10}H_9N_5OS_2$: C, 43.00; H, 3.25; N, 25.07; S, 22.96. Found: C, 42.89; H, 3.30; N, 25.15; S, 22.89; MS (ES *m/z*): 280 $[M+1]^+$.

***3-(Butylthio)-6-(5-methylisoxazol-3-yl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole (4d).*** Yield: (77%); mp 109–111°C; IR (KBr $cm^{-1}$) 1592 (C═N); 1259 (C–O–N); 1187 (S–C); $^1$H-NMR (DMSO-$d_6$; δ ppm): 0.88 (t, $J=7.4$ Hz, 3H, –$CH_3$); 1.37–1.46 (m, 2H, –$CH_2$); 1.63–1.70 (m, 2H, –$CH_2$); 2.55 (S, 3H, Ar–$CH_3$); 3.23 (t, $J=7.2$ Hz, 2H, S–$CH_2$); 7.01 (S, 1H, Ar–H) $^{13}$C-NMR (DMSO-$d_6$, δ ppm): 11.86; 13.27; 20.88; 31.20; 32.22; 99.99; 142.34; 153.74; 155.26; 156.75; 173.05; *Anal*. Calcd for $C_{11}H_{13}N_5OS_2$: C, 44.73; H, 4.44; N, 23.71; S, 21.71. Found: C, 44.67; H, 4.38; N, 23.78; S, 21.66; MS (ES *m/z*): 318.02 $[M+Na]^+$ 100%; 296.01 $[M+1]^+$.

***2-(6-(5-Methylisoxazol-3-yl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-3-ylthio)acetic acid (4e).*** Yield: (75%); mp 249–251°C; IR (KBr $cm^{-1}$) 3406 (−OH); 1697 (–C═O); 1606 (C═N); 1245 (C–O–N) ; 1196 (S–C); $^1$H-NMR (DMSO-$d_6$; δ ppm): 2.55 (S, 3H,–$CH_3$); 3.85 (S, 2H,–S–$CH_2$); 7.02 (S, 1H, Ar–H); 12.46 (S, 1H, –OH); *Anal*. Calcd for $C_9H_7N_5O_3S_2$: C, 36.36; H, 2.37; N, 23.56; S, 21.57. Found: C, 36.33; H, 2.31; N, 23.52; S, 21.63; MS (ES *m/z*): 319.88 $[M+Na]^+$ 100% ; 297.89 $[M+1]^+$.

***3-(Benzylthio)-6-(5-methylisoxazol-3-yl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole (4f).*** Yield: (85%); mp 220–222°C; IR (KBr $cm^{-1}$) 1684 (–C═O); 1609 (C═N); 1235 (C–O–N) ; 1186 (S–C); $^1$H-NMR (DMSO-$d_6$; δ ppm): 2.56 (S, 3H,–$CH_3$); 4.47 (S, 2H, –S–$CH_2$); 6.99 (S, 1H, Ar–H); 7.22–7.33 (m, 5H, –Ar–H); $^{13}$C-NMR (DMSO-$d_6$, δ ppm): 12.38; 37.75; 99.73; 127.89; 128.64; 129.08; 135.97; 143.17; 154.14; 155.35; 156.80; 172.23; *Anal*. Calcd for $C_{14}H_{11}N_5OS_2$: C, 51.05; H, 3.37; N, 21.26; S, 19.47. Found: C, 51.16; H, 3.29; N, 21.31; S, 19.41; MS (LC-MS *m/z*): 330 $[M+1]^+$ 100%.

***2-(6-(5-Methylisoxazol-3-yl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-3-ylthio)-1-phenylethanone (4g).*** Yield: (88%); mp 172–174°C; IR (KBr $cm^{-1}$) 1680 (C═O); 1602 (C═N); 1257 (C–O–N); 1194 (S–C); $^1$H-NMR (DMSO-$d_6$; δ ppm): 2.57 (S, 3H, –$CH_3$); 4.97 (S, 2H, –S–$CH_2$); 6.62 (S, 1H, Ar–H); 7.48–7.52 (m, 2H, Ar–H); 7.60–7.65 (m, 1H, Ar–H); 8.02 (t, $J=7.2$ Hz, 2H, Ar–H); $^{13}$C-NMR (DMSO-$d_6$, δ ppm): 11.84; 40.17; 99.90; 128.33; 128.65; 133.65; 134.92; 141.67; 153.72; 155.11; 156.75; 172.82; 192.90; *Anal*. Calcd for $C_{15}H_{11}N_5O_2S_2$: C, 50.41; H, 3.10; N, 19.59; S, 17.94. Found: C, 50.52; H, 3.05; N, 19.52; S, 17.99; MS (ES *m/z*): 379.93 $[M+Na]^+$ 100%; 357.94 $[M+1]^+$.

***2-(6-(5-Methylisoxazol-3-yl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-3-ylthio)-1-(4-chlorophenyl)ethanone (4h).*** Yield: (85%); mp 184–186°C; IR (KBr $cm^{-1}$) 1694 (–C═O); 1592 (C═N); 1261 (C–O–N); 1200 (S–C); $^1$H-NMR (DMSO-$d_6$; δ ppm): 2.55 (S, 3H,–$CH_3$); 4.99 (s, 2H, S–$CH_2$); 6.90 (S, 1H, Ar–H); 7.63 (d, $J=8.4$ Hz, 2H, Ar–H,); 8.02 (d, $J=8.4$ Hz, 2H, Ar–H); *Anal*. Calcd for $C_{15}H_{10}ClN_5O_2S_2$: C, 45.98; H, 2.57; N, 17.87; S, 16.37. Found: C, 45.90; H, 2.64; N, 17.82; S, 16.31; MS (ES *m/z*): 413.90 $[M+Na]^+$ 100%; 391.93 $[M+1]^+$.

***2-(6-(5-Methylisoxazol-3-yl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-3-ylthio)-1-(4-bromophenyl)ethanone (4i).*** Yield: (90%); mp 198–200°C; IR (KBr $cm^{-1}$) 1679 (–C═O); 1586 (C═N); 1257 (C–O–N); 1193 (S–C); $^1$H-NMR (DMSO-$d_6$; δ ppm): 2.55 (S, 3H, –$CH_3$); 4.98 (s, 2H, S–$CH_2$); 6.89 (S, 1H, Ar–H); 7.77 (d, $J=8.4$ Hz, 2H, Ar–H); 7.94 (d, $J=8.4$ Hz, 2H, Ar–H); $^{13}$C-NMR (DMSO-$d_6$, δ ppm): 11.92; 40.10; 100.01; 127.99; 130.45; 131.88; 134.03; 141.53; 153.92; 155.23; 156.91; 173.08; 192.52; *Anal*. Calcd for $C_{15}H_{10}BrN_5O_2S_2$: C, 41.29; H, 2.31; N, 16.05; S, 14.70. Found: C, 41.35; H, 2.26; N, 15.97; S, 14.76; MS (ES *m/z*): 459.86 $[M+Na]^+$ 100%; 457.83; 435.86 $[M^+]$; 437.87 $[M+2]^+$.

***2-(6-(5-Methylisoxazol-3-yl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-3-ylthio)-1-p-tolylethanone (4j).*** Yield: (80%); mp 183–185°C; IR (KBr $cm^{-1}$) 1675 (−C═O); 1601 (C═N); 1255 (C–O–N); 1190 (S–C); $^1$H-NMR (DMSO-$d_6$; δ ppm): 2.42 (s, 3H, –$CH_3$); 2.57 (S, 3H, –$CH_3$); 4.94 (s, 2H, S–$CH_2$); 6.62 (s, 1H, Ar–H); 7.28 (d, $J=8$ Hz, 2H, Ar–H,); 7.91 (d, $J=8$ Hz, 2H, Ar–H); $^{13}$C-NMR (DMSO-$d_6$, δ ppm): 11.86; 21.12; 40.20; 99.98; 128.52; 129.29; 132.48; 141.70; 144.34; 153.81; 155.21; 156.80; 173.02; 192.63; *Anal*. Calcd for $C_{16}H_{13}N_5O_2S_2$: C, 51.74; H, 3.53; N, 18.85; S, 17.27. Found: C, 51.66; H, 3.47; N, 18.91; S, 17.34; MS (ES *m/z*): 394.00 $[M+Na]^+$ 100%; 371.99 $[M+1]^+$.

***2-(6-(5-Methylisoxazol-3-yl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-3-ylthio)-1-(4-methoxyphenyl)ethanone (4k).*** Yield: (93%); mp 180–182°C; IR (KBr $cm^{-1}$) 1673 (–C═O); 1599 (C═N); 1258 (C–O–N); 1180 (S–C); $^1$H-NMR ($CDCl_3$; δ ppm): 2.56 (s, 3H, –$CH_3$); 3.88 (S, 3H, –O–$CH_3$); 4.93 (s, 2H, S–$CH_2$); 6.62 (s, 1H, Ar–H); 6.95 (d, $J=7.2$ Hz, 2H, Ar–H,); 7.20 (d, $J=7.2$ Hz, 2H, Ar–H); *Anal*. Calcd for $C_{16}H_{13}N_5O_3S_2$: C, 49.60; H, 3.38; N, 18.08; S, 16.55. Found: C, 49.72; H, 3.31; N, 18.12; S, 16.60; MS (ES *m/z*): 388 $[M+1]^+$ 100%.

***1-Biphenyl-4-yl-2-[6-(5-methylisoxazol-3-yl)[1,2,4]triazolo[3,4b][1,3,4]thiadiazol-3-ylsulfanyl]-ethanone (4l).*** Yield: (87%); mp 197–199°C; IR (KBr $cm^{-1}$) 1672 (–C═O); 1601 (C═N); 1260 (C–O–N); 1194 (S–C); $^1$H-NMR (DMSO-$d_6$ δ ppm): 2.51 (s, 3H, –$CH_3$); 5.03 (s, 2H, –$CH_2$); 6.88 (s, 1H, Ar–H); 7.44 (t, $J=7.4$ Hz, 1H, Ar–H,); 7.52 (t, $J=7.6$ Hz, 2H, Ar–H); 7.76 (d, $J=8$ Hz, 2H, Ar–H); 7.85 (d, $J=7.6$ Hz, 2H, Ar–H); 8.09 (d, $J=8$ Hz, 2H, Ar–H) $^{13}$C-NMR (DMSO-$d_6$, δ ppm): 11.87;

40.15; 100.01; 126.92; 126.97; 128.50; 129.07; 129.20; 133.78; 138.64; 141.65; 145.10; 153.89; 155.23; 156.86; 173.04; 192.75; *Anal*. Calcd for $C_{21}H_{15}N_5O_2S_2$: C, 58.18; H, 3.49; N, 16.16; S, 14.79. Found: C, 58.24; H, 3.54; N, 16.02; S, 14.84; MS (ES *m/z*): 433.98 $[M+1]^+$ 100%.

***2-(6-(5-Methylisoxazol-3-yl)-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazol-3-ylthio)-1-(4-nitrophenyl) ethanone (4m).*** Yield: (86%); mp 201–203°C; IR (KBr $cm^{-1}$) 1699 (–C═O); 1601 (C═N); 1257 (C–O–N); 1198 (S–C); $^1$H-NMR (DMSO-$d_6$; δ ppm): 2.55 (S, 3H, $–CH_3$); 5.06 (s, 2H, $–CH_2$); 6.93 (S, 1H, Ar–H); 8.24 (d, $J = 8$ Hz, 2H, Ar–H); 8.36 (d, $J = 7.6$ Hz, 2H, Ar–H); *Anal*. Calcd for $C_{21}H_{15}N_5O_2S_2$: C, 44.77; H, 2.50; N, 20.88; S, 15.94. Found: C, 44.68; H, 2.56; N, 20.92; S, 15.90; MS (ES *m/z*): 424.94 $[M+Na]^+$ 100%; 402.95 $[M+1]^+$.

**Acknowledgments.** We are grateful to the Director, N.I.T. Warangal for providing the facilities. One of the authors Krishnaiah thanks U.G.C. New Delhi, Govt. of India for the award of UGC-Junior Research Fellowship.

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