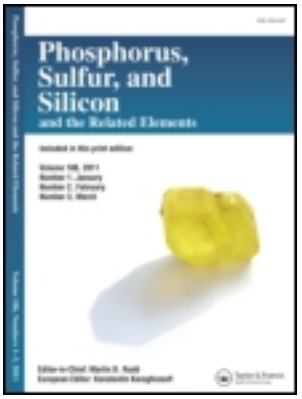

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gpss20

Three-Component Reaction: Synthesis, Characterization, and Biological Study of Some Fused Bridgehead Nitrogen Heterocyclic Systems Containing 4-Methylthiophenyl Moiety

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Version of record first published: 07 Mar 2011.

To cite this article: K. Manjunatha, Boja Poojary, Prajwal L. Lobo, N. Suchetha Kumari & C. Anoop (2011): Three-Component Reaction: Synthesis, Characterization, and Biological Study of Some Fused Bridgehead Nitrogen Heterocyclic Systems Containing 4-Methylthiophenyl Moiety, Phosphorus, Sulfur, and Silicon and the Related Elements, 186:3, 526-532

To link to this article: http://dx.doi.org/10.1080/10426507.2010.506454

Phosphorus, Sulfur, and Silicon, 186:526–532, 2011

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426507.2010.506454

THREE-COMPONENT REACTION: SYNTHESIS, CHARACTERIZATION, AND BIOLOGICAL STUDY OF SOME FUSED BRIDGEHEAD NITROGEN HETEROCYCLIC SYSTEMS CONTAINING 4-METHYLTHIOPHENYL MOIETY

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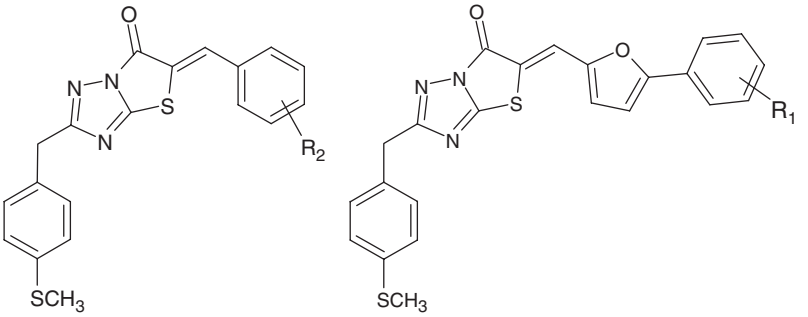
GRAPHICAL ABSTRACT



Abstract *Several substituted thiazolo-[3,2-b]-1,2,4-triazole derivatives **4** were synthesized by a one-pot, three-component reaction of 3-(4-methylthiobenzyl)-1,2,4-triazole-5-thiol **3**, substituted 5-aryl-furan-2-carboxaldehydes/substituted aromatic aldehydes, and monochloroacetic acid in acetic acid using acetic anhydride and anhydrous sodium acetate. Compound **3** was obtained from 4-methylthiophenyl acetic acid by esterification followed by hydrazinolysis. All structures of the newly synthesized compounds were elucidated by elemental analysis and spectral data. The newly synthesized compounds were also screened for their antimicrobial and anti-inflammatory activities.*

Supplemental materials are available for this article. Go to the publisher's online edition of Phosphorus, Sulfur, and Silicon and the Related Elements *to view the free supplemental file.*

Keywords Anti-inflammatory activity; antimicrobial activity; 4-methylthiobenzyl; three component reaction; 1,2,4-triazole-5-thiol

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INTRODUCTION

Multicomponent reactions (MCRs) are fundamentally different from two-component reactions in several aspects. Convergent synthetic pathways generally show advantages over linear or divergent approaches with respect to speed, time, yield, and reproducibility. Among organic reactions, MCRs are highly convergent.[1] MCRs with more than two starting materials are assembled to afford a complex product. Therefore, they constitute a superior tool for diversity-oriented, complexity-oriented, and complexity-generating synthesis for drug discovery.[2] MCRs being one-pot reactions, they are practically single-step conversions and are easier to carry out compared to multistep synthesis.

Thiazoles are an important class of heterocyclic compounds, found in many potent biologically active molecules such as fentiazac and meloxicam[3,4] (both anti-inflammatory agents), nizatidine[5] (antiulcerative agent), and sulfathiazole (antibacterial agent). Thiazoles represent an interesting class of compounds possessing a wide spectrum of biological activities such as anti-inflammatory, antimicrobial,[6,7] antitumor,[8] anticonvulsant,[9] analgesic,[10] and anticancer[11] properties. It has been also reported that derivatives of 1,2,4-triazole and their condensed nucleus systems exert diverse pharmacological activities such as antimicrobial, anti-inflammatory,[12–14] anticancer,[15] and antitubercular[16] properties. Certain 1,2,4-triazoles also find applications in the preparation of photographic plates and polymers, and as analytical agents.[17]

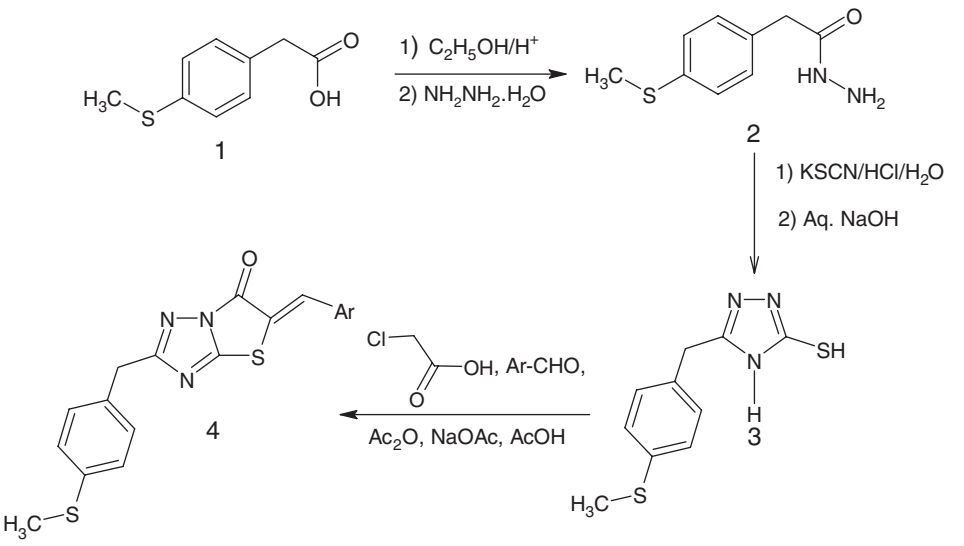
A review of the literature revealed that the presence of 4-methylthiophenyl moiety[18] is found to increase the biological activity of the molecules. A few heterocyclic analogues containing N-bridged heterocycles bearing 4-methylthiophenyl moiety possess good anti-inflammatory[18,19] and antimicrobial[20,21] activities.

Prompted by these chemical reactivities and broad spectrum of biological activity, we report in this article the synthesis of some fused bridgehead nitrogen heterocyclic systems, viz., substituted thiazolo-[3,2-*b*]-1,2,4-triazole derivatives incorporating 4-methylthiophenyl moiety using a multicomponent synthesis, and we also screen them for antimicrobial and anti-inflammatory activities.

RESULTS AND DISCUSSION

3-(4-Methylthiobenzyl)-1,2,4-triazole-5-thiol **3** was synthesized according to the procedure reported in the literature.[22] The condensation of **3** with monochloroacetic acid and 5-aryl-furan-2-carbaldehydes/substituted benzaldehydes in the presence of acetic anhydride, acetic acid, and anhydrous sodium acetate afforded substituted thiazolo-[3,2-*b*]-1,2,4-triazole derivatives **4** (Scheme 1). Substituted 5-aryl-furan-2-carbaldehydes were prepared through a Meerwein reaction.[23]

The structures of the newly synthesized compounds were confirmed by elemental analysis, IR, ^{1}H NMR, and mass spectrometry. Characterization data of all the newly synthesized compounds are presented in Table 1. The ^{1}H NMR spectrum of **3** showed a down-field D_2O exchangeable broad singlet at δ 13.30 ppm for its two tautomeric NH/SH protons and a singlet at δ 2.41 ppm is assigned to the protons of SCH_3 group. Also a singlet at δ 3.83 ppm appeared for its benzylic CH_2 group. The four protons of 4-methylthiobenzyl moiety appeared as two distinct doublets centered at $\delta = 7.18$ and $\delta = 7.20$ ppm, respectively, with a coupling constant $J = 7.2$ Hz. Further, the LC-MS spectrum of **3** showed the molecular ion peak at m/z 237, which corresponds to its molecular formula, $C_{10}H_{11}N_3S_2$.



Ar = 5-(4-Cl-C_6H_4)furan-2-yl, 5-(4-NO_2-C_6H_4)furan-2-yl, 2-(2-NO_2-C_6H_4)furan-2-yl, 5-(4-Br-C_6H_4)furan-2-yl, 5-(2,4,5-Cl_3-C_6H_2)furan-2-yl, 5-(3-Cl-4-F-C_6H_3)furan-2-yl, 5-(2-Me-6-NO_2-C_6H_3)furan-2-yl, 5-(2-Me-4-NO_2-C_6H_3)furan-2-yl, 5-(4-Cl-2-NO_2-C_6H_3)furan-2-yl, 5-(2,4-Cl_2-C_6H_3)furan-2-yl, 3,4-$(OCH_3)_2$-C_6H_3, 3,4-$(OCH_3)_2$-5-NO_2-C_6H_2, 4-OH-C_6H_4, 3,5-F_2-C_6H_3.

Scheme 1

In the IR spectra of **4a–n**, all compounds displayed strong absorption bands in the regions 1759–1724 cm^{-1} (C=O) and 1628–1592 cm^{-1} (C=N), respectively. The absorption bands associated with other functional groups appeared in the expected regions. The absence of signals due to two protons of tautomeric NH/SH in ^1H NMR spectra of **4a–n** and the

Table 1 Characterization data of compounds **4a–n**

Compound	Ar	Molecular formula	Melting point (°C)	Yield (%)
4a	5-(4-Cl−C_6H_4)furan-2-yl	$C_{23}H_{16}ClN_3O_2S_2$	196–198	71
4b	5-(4-NO_2−C_6H_4)furan-2-yl	$C_{23}H_{16}N_4O_4S_2$	250–252	75
4c	5-(2-NO_2−C_6H_4)furan-2-yl	$C_{23}H_{16}N_4O_4S_2$	150–152	69
4d	5-(4-Br−C_6H_4)furan-2-yl	$C_{23}H_{16}BrN_3O_2S_2$	173–175	72
4e	5-(2,4,5-Cl_3−C_6H_2)furan-2-yl	$C_{23}H_{14}Cl_3N_3O_2S_2$	208–210	76
4f	5-(3-Cl-4-F−C_6H_3)furan-2-yl	$C_{23}H_{15}ClFN_3O_2S_2$	200–202	80
4g	5-(2-Me-6-NO_2−C_6H_3)furan-2-yl	$C_{24}H_{18}N_4O_4S_2$	224–226	69
4h	5-(2-Me-4-NO_2−C_6H_3)furan-2-yl	$C_{24}H_{18}N_4O_4S_2$	168–170	78
4i	5-(4-Cl-2-NO_2−C_6H_3)furan-2-yl	$C_{23}H_{15}ClN_4O_4S_2$	215–217	70
4j	5-(2,4-Cl_2−C_6H_3)furan-2-yl	$C_{23}H_{15}Cl_2N_3O_2S_2$	144–146	64
4k	3,4-$(OCH_3)_2$−C_6H_3	$C_{21}H_{19}N_3O_3S_2$	158–160	67
4l	3,4-$(OCH_3)_2$-5-NO_2−C_6H_2	$C_{21}H_{18}N_4O_5S_2$	167–169	72
4m	4-OH−C_6H_4	$C_{19}H_{15}N_3O_2S_2$	120–124	70
4n	3,5-F_2−C_6H_3	$C_{19}H_{13}F_2N_3OS_2$	161–163	65

presence of a new singlet in the region δ, 7.78–8.24 ppm for the exocyclic methyne proton of the thiazolidinone ring confirmed the transformation of **3** into the corresponding substituted thiazolo-[3,2-*b*]-1,2,4-triazole derivatives **4a–n**. Two distinct doublets observed for **4a–j** in their ^{1}H NMR spectra in the region δ, 6.92–7.00 ppm with a coupling constant value $J =$ 3.6–4.2 Hz (β-protons of furan ring) also confirmed their structures. Furthermore in the ^{13}C NMR spectra, **4a–n** showed their characteristic -C=O carbon signal in the region δ, 176–179.1 ppm in addition to other characteristic signals of the remaining carbon atoms.

BIOLOGICAL ACTIVITY

Anti-Inflammatory Activity

The anti-inflammatory activity of the 15 newly synthesized compounds was determined by the carrageenan induced paw edema method.[24] The results of anti-inflammatory activity are summarized in Table S1 (Supplemental Materials, available online).

Antimicrobial Activity

The newly synthesized compounds were screened for their antibacterial activity against *Staphylococcus aureus* (ATTC-25923), *Escherichia coli* (ATTC-25922), *Pseudomonas aeruginosa* (ATTC-27853), and *Klebsiella pneumoniae* (recultured) bacterial strains by a serial plate dilution method.[25,26] The newly prepared compounds were also screened for their antifungal activity against *Aspergillus flavus* (NCIM No. 524), *Aspergillus fumigatus* (NCIM No. 902), *Penicillium marneffei* (recultured), and *Trichophyton mentagrophytes* (recultured) in DMSO by a serial plate dilution method.[27,28] The results of antimicrobial activity are summarized in Tables S2 and S3 (Supplemental Materials).

CONCLUSION

We report the synthesis of substituted thiazolo-[3,2-*b*]-1,2,4-triazole derivatives by making use of a three-component reaction protocol that resulted in good yields, and we also report their pharmacological activities. Among the screened compounds for anti-inflammatory activity, **4m**, which contains a 4-hydroxyphenyl group as substituent, exhibited the highest activity. Similarly, all the compounds tested for antimicrobial activity showed moderate to good activity against the pathogenic strains. However, compounds **4a**, **4c**, and **4f** showed good activity against all the bacterial strains. The good activity can be attributed to the presence of pharmacologically active (4-chloro-phenyl)furyl, (2-nitrophenyl)furyl, and (3-chloro-4-fluro-phenyl)furyl groups. On the other hand, compound **4a** containing 4-chlorophenyl moiety attached to furyl ring showed good activity against all the tested fungal strains.

EXPERIMENTAL

The melting points were determined by an open capillary method and are uncorrected. The IR spectra (in KBr pellets) were recorded on a Shimadzu FT-IR 157 spectrophotometer. The ^{1}H NMR spectra were recorded ($CDCl_3$/DMSO-d_6 mixture) on a Bruker Avance II-400 (400 MHz) spectrometer using TMS as an internal standard. Mass spectra were recorded on a Finnigan MAT8230 mass spectrometer. Elemental analysis (CHNS) was performed

on the CHNS Elementar Vario EL III. The progress of the reaction was monitored by TLC on silica gel plates.

Procedure for the Preparation of 4-Methylthiophenyl-Acetic Acid Hydrazide (2)

The mixture of ethyl ester of 4-methythiophenyl acetic acid **1** (0.1 mol) and hydrazine hydrate (0.2 mol) was refluxed in absolute alcohol (50 mL) for 8 h. The excess solvent was then distilled off under reduced pressure, and the concentrated solution was quenched with ice cold water. The solid that separated was filtered, washed, and dried. The crude product was purified by recrystallization from ethanol to give 89% of **2** with mp 136–138°C (colorless). IR (KBr, cm^{-1}): 3344 (NH, NH_2), 3203 (NH_2), 2963 (C—H), 1622 (CO—NH);^{1}H NMR (400 MHz, $CDCl_3$, δ): 2.49 (s, 3H, SCH_3), 3.53 (s, 2H, CH_2), 3.82 (br-s, 2H, NH_2), 6.67 (br-s, 1H, NH), 7.18 (d, Ar-H, $J = 8.4$ Hz), 7.26 (d, Ar—H, $J = 8.4$ Hz); LC-MS (m/z): 196 (M^+), Anal. Calcd. (%) for $C_9H_{12}N_2OS$: C55.09, H6.16, N14.27. S 16.34, Found: C55.06, H6.15, N14.20, S16.26.

Procedure for the Preparation of 3-(4-Methylthiobenzyl)-1,2,4-triazole-5-thiol (3)

4-Methylthiophenyl–acetic acid hydrazide (**2**) (0.1 mol) was dissolved in water (100 mL) containing concentrated hydrochloric acid (10 mL). Potassium thiocyanate (0.2 mol) was added, and the mixture was warmed on a water bath for 5 h. The reaction mixture was cooled. The precipitated solid was filtered, dried, and recrystallized from ethanol to get 4-methylthiophenylacetyl thiosemicarbazide. A mixture of resulting thiosemicarbazide (0.01 mol) and sodium hydroxide (5%, 100 mL) was refluxed on a heating mantle for 3 h. The reaction mixture was poured into crushed ice and acidified with dilute hydrochloric acid. The precipitate thus obtained was filtered, dried, and recrystallized from ethanol to obtain 85% of **3** with mp 195–197°C (colorless solid). IR (KBr, cm^{-1}): 3154 (NH), 1206 (C=S); ^{1}H-NMR(DMSO-*d*6, δ): 2.49 (s, 3H, SCH_3), 3.53 (s, 2H, CH_2), 7.18 (d, Ar-H, $J = 8.4$ Hz), 7.26 (d, Ar-H, $J = 8.4$ Hz), 13.30 (brs, 2H, NH/SH); ^{13}C NMR (100 MHz, $CDCl_3$, δ): 16.1, 32.1, 127.5, 128.5, 131.9, 139.2, 152.6, 167.1; LC-MS (m/z): 237 (M^+); Anal. Calcd. (%) for $C_{10}H_{11}N_3S_2$: C50.60, H4.67, N17.70, S27.02, Found: C50.56, H4.71, N17.79, S27.05.

General Procedure for the Preparation of 2-(4-Methylthiobenzyl-7-(5-aryl-2-furylidine/substituted benzylidene)-thiazolo[3,2-*b*]-1,2,4-trizol-5(6*H*)-ones (4)

A mixture of 3-(4-methylthiobenzyl)-1,2,4-triazole-5-thiol **3** (0.01 mol), monochloroacetic acid (0.015 mol), 5-aryl-furan-2-carbaldehyde/substituted aromatic aldehydes (0.01 mol), acetic anhydride (15 mL), and anhydrous sodium acetate (2 g) in glacial acetic acid (20 mL) was heated to reflux for 6–8 h. The reaction mixture was cooled and poured onto crushed ice with vigorous stirring. The solid obtained was filtered, washed with water, dried, and recrystallized from a mixture ethanol and dimethyl formamide.

2-(4-Methylthiobenzyl-7-(4-chloro-phenyl-2-furylidine)-thiazolo[3,2-*b*]-1, 2,4-trizol-(6*H*)-one (4a). IR (KBr, cm^{-1}): 3073 (Ar—H), 2943 (C—H), 1751 (C=O),

1596 (C=N); ^{1}H NMR (DMSO-*d*6, *δ)*: 2.44 (s, 3H, SCH_3), 4.02 (s, 2H, CH_2), 7.22 (d, 2H, 4-methylthiobenzyl, $J = 8$ Hz), 7.30 (d, 2H, 4-methylthiobenzyl, $J = 8$ Hz), 7.33 (d, 1H, furan H, $J = 3.6$ Hz), 7.48 (d, 1H, furan H, $J = 3.6$ Hz), 7.58–7.96 (m, 4H, 4-chlorophenyl), 7.96 (s, 1H, exocyclic methyne-H); LC-MS (m/z): 466 (M^++1);^{13}C NMR (100 MHz, $CDCl_3$, *δ*): 16.1, 32.1, 112.5, 116.1, 126.3, 126.9, 127.5, 128.2, 129.4, 130.4, 131.9, 139.2, 151.0, 152.6, 167.1, 177.6; Anal. Calcd. (%) for $C_{23}H_{16}N_3ClO_2S_2$: C59.28, H3.46, N9.02, S13.76, Found: C59.32, H3.42, N9.05, S13.80.

2-(4-Methylthiobenzyl-7-(4-nitro-phenyl-2-furylidine)-thiazolo[3,2-*b*]-1, 2,4-trizol-(6*H*)-one (4b). IR (KBr, cm^{-1}): 3073 (Ar—H), 2920 (C-H), 1734 (C=O), 1612 (C=N). ^{1}H-NMR (DMSO-d_6, *δ*): 2.45 (s, 3H, SCH_3), 4.00 (s, 2H, CH_2), 7.20 (d, 2H, 4-methylthiobenzyl, $J = 8.4$ Hz), 7.29 (d, 2H, 4-methylthiobenzyl, $J = 8.0$ Hz), 7.42 (d, 1H, furan H, $J = 4$ Hz), 7.53 (d, 1H, furan H, $J = 4$ Hz), 8.12 (d, 2H, 4-nitrophenyl, $J = 8.8$ Hz), 8.35 (d, 2H, 4-nitrophenyl, $J = 8.8$ Hz), 8.13 (s, 1H, exocyclic methyne-H); LC-MS (m/z): 477 (M^++1); ^{13}C NMR (100 MHz, $CDCl_3$, *δ*): 16.1, 32.5, 114.2, 117.6, 126.7, 126.9, 127.3, 127.6, 129.8, 131.0, 132.4, 140.2, 151.4, 152.8, 168.2, 178.7; Anal. Calcd. (%) for $C_{23}H_{16}N_4O_4S_2$: C57.97, H3.38, N11.76, S13.46, Found: C57.94, H3.42, N11.73, S13.49.

2-(4-Methylthiobenzyl-7-(4-bromo-phenyl-2-furylidine)-thiazolo[3,2-*b*]-1,2,4-trizol-(6*H*)-one (4d). IR (KBr, cm^{-1}): 3036 (Ar—H), 2923 (C—H), 1732 (C=O), 1608 (C=N), 853 (C-Br); ^{1}H NMR (DMSO-d_6, *δ*): 2.46 (s, 3H, SCH_3), 3.98 (s, 2H, CH_2), 7.12 (d, 1H, furan H, $J = 3.6$ Hz), 7.26 (d, 1H, furan H, $J = 3.6$ Hz), 7.18 (d, 2H, 4-methylthiobenzyl, $J = 8.4$ Hz), 7.33 (d, 2H, 4-methylthiobenzyl, $J = 8$ Hz), 7.48 (d, 2H, 4-bromophenyl, $J = 8$ Hz), 7.64 (d, 2H, 4-nitrophenyl, $J = 8$ Hz), 8.05 (s, 1H, exocyclic methyne-H); LC-MS (m/z): 509 (M^++1); ^{13}C NMR (100 MHz, $CDCl_3$, *δ*): 16.9, 34.6, 111.5, 116.7, 126.1, 126.46, 127.4, 128.1, 129.8, 130.9, 131.5, 149.0, 151.1, 152.6, 169.2, 177.4; Anal. Calcd. (%) for $C_{23}H_{16}N_3BrO_2S_2$: C54.12, H3.16, N7.86, S11.89, Found: C54.20, H3.12, N7.78, S11.80.

2-(4-Methylthiobenzyl-7-(3,4-dimethoxy-benzylidine)-thiazolo[3,2-*b*]-1, 2,4-trizol-(6*H*)-one (4k). IR (KBr, cm^{-1}): 3084 (Ar—H), 2924 (C-H), 1732 (C=O), 1587 (C=N); ^{1}H NMR (DMSO-d_6, *δ*): 2.54 (s, 3H, SCH_3), 3.86–3.87 (2s, 6H, 2xOCH_3), 4.48 (s, 2H, CH_2), 7.18 (d, 2H, 4-methylthiobenzyl, $J = 8.4$ Hz), 7.37 (d, 2H, 4-methylthiobenzyl, $J = 8.4$ Hz), 7.47–7.68 (m, 3H, dimethoxyphenyl), 7.86 (s, 1H, exocyclic methyne-H); LC-MS (m/z): 426 (M^+); ^{13}C NMR (100 MHz, $CDCl_3$, *δ*): 16.8, 32.0, 57.6, 57.7, 124.8, 126.3, 126.0, 128.4, 128.5, 129. 4, 130.7, 131.8, 139.1, 151.0, 152.1, 167.0, 169.6, 178.2; Anal. Calcd. (%) for $C_{21}H_{19}N_3O_3S_2$: C59.27, H4.50, N9.87, S15.07, Found: C59.32, H4.55, N9.92, S15.02.

2-(4-Methylthiobenzyl-7-(3,5-difluoro-benzylidine)-thiazolo[3,2-*b*]-1,2,4-trizol-(6*H*)-one (4n). IR (KBr, cm^{-1}): 3045 (Ar—H), 2961(C-H), 1724 (C=O); ^{1}H NMR (DMSO-d_6, *δ*): 2.49 (s, 3H, SCH_3), 4.52 (s, 2H, CH_2), 7.21 (d, 4-methylthiobenzyl, $J =$ 7.8 Hz), 7.34 (d, 2H, 4-methylthiobenzyl, $J = 7.6$ Hz), 7.65–7.86 (m, 3H, difluorophenyl), 8.03 (s, 1H, exocyclic methyne-H); LC-MS (m/z): 402 (M^+); ^{13}C NMR (100 MHz, $CDCl_3$, *δ*): 16.2, 32.0, 126.2, 126.6, 127.8, 127.2, 129.3, 129.0, 130.1, 141.4, 149.5, 151.3, 152.6, 168.5, 169.4, 177.4; Anal.Calcd.(%) for $C_{19}H_{13}N_3OS_2$: C56.84, H3.26, N10.47, S15.97, Found: C56.88, H3.22, N10.54, S15.92.

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