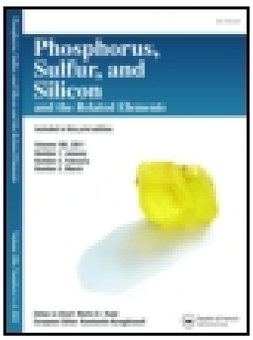

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One-pot synthesis of sulfonyl-1*H*-1,2,3-triazolyl-thiomorpholine 1,1-dioxide derivatives and evaluation of their biological activity

Rakesh Sreerama[a], Narasimha Swamy T.[a], Ravinder M.[a], Vasudeva Reddy N.[b], and Sirassu Narsimha[a]

[a]Department of Chemistry, Chaitanya Deemed to be University, Warangal, Telangana, India; [b]Department of Chemistry, Kakatiya University, Warangal, Telangana, India

ABSTRACT

A one-pot procedure for the synthesis of novel 1,2,3-triazole derivatives (**5a–5l**) in good yields (63 to 77%) using different sulfonic acids and 4-(prop-2-yn-1-yl)thiomorpholine 1,1-dioxide through the *in situ* generated sulfonyl azides was developed. The structures of the newly synthesized compounds were confirmed by ^{1}H NMR, ^{13}C NMR, mass spectrometry, and elemental analysis. The newly synthesized compounds were screened for *in vitro* antibacterial activity and free radical scavenging activity in terms of hydrogen donating or radical scavenging ability by the DPPH method. Among all, the compound *N*-(4-((4-((1,1-dioxidothiomorpholino) methyl)-1H-1,2,3-triazol-1-yl)sulfonyl)phenyl) acetamide (**5l**) was found to exhibit potent activity as compared to the standard drugs.

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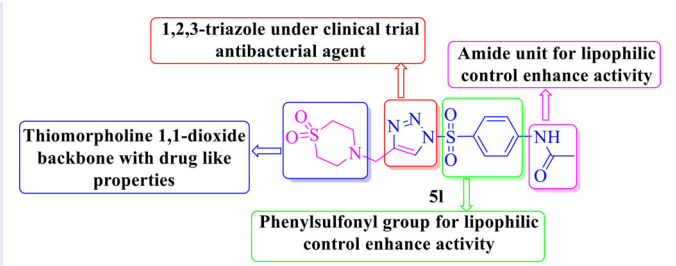
1,2,3-triazole; thiomorpholine; sulfonyl azides; antibacterial activity; antioxidant activity

GRAPHICAL ABSTRACT



Introduction

An increased resistance of pathogenic microorganisms toward the currently existing antibiotic drugs is a major concern to public health organizations around the world. Bacteria are microscopic unicellular organisms and most of them are harmless to humans and some strains are even beneficial.[1] However, various types of bacteria are pathogenic and can cause serious infectious diseases.[2] Therefore, the treatment of microbial infections caused by microbiologically resistant pathogens becomes an important public health concern.[3] This has resulted in a significant need for the development of new and more powerful antimicrobial agents with a wide range of inhibitory activity, effectiveness, and low toxicity. Thus, an effective approach to the development of new antimicrobial agents with new mechanisms of action and structural modification is required to improve their target selectivity and effectiveness.

The high therapeutic properties of the sulfonyl group containing drugs have encouraged medicinal chemists to synthesize a large variety of novel chemotherapeutic agents.[4] As well, the 1,2,3-triazoles and their derivatives are of great importance because of their wide applications in medical, pharmaceutical, biochemical, and material sciences.[5] On the other hand, the sulfonylazides are resourceful reagents for a plethora of organic transformations which drives welloutside the usually employed diazo[6] as well as azide transfer reactions.[7] They have also been utilized as valuable reagents in the synthesis of α-diazocarbonyl reagents,[8] the olefins hydroazidation and aziridation,[9] the radical amination,[10] and metal-promoted coupling reactions.[11]

Consequently, several methodologies have been developed for the synthesis of sulfonylazides.[12] However, to the best of our knowledge, no report was available about the use of *in situ* generated sulfonylazides to sulfonyl-1*H*-1,2,3-triazoles in the literature. In view of the sustainable chemical synthesis, herein, we synthesized some new biologically active sulfonyl-1*H*-1,2,3-triazolyl-thiomorpholine 1,1-dioxide derivatives (**5a–5l**) using

CONTACT Sirassu Narsimha narsimha.s88@gmail.com Department of Chemistry, Chaitanya Deemed to be University, Warangal, Telangana 506 001, India
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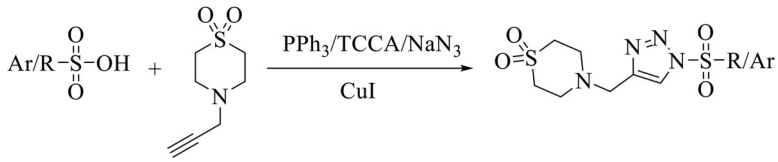
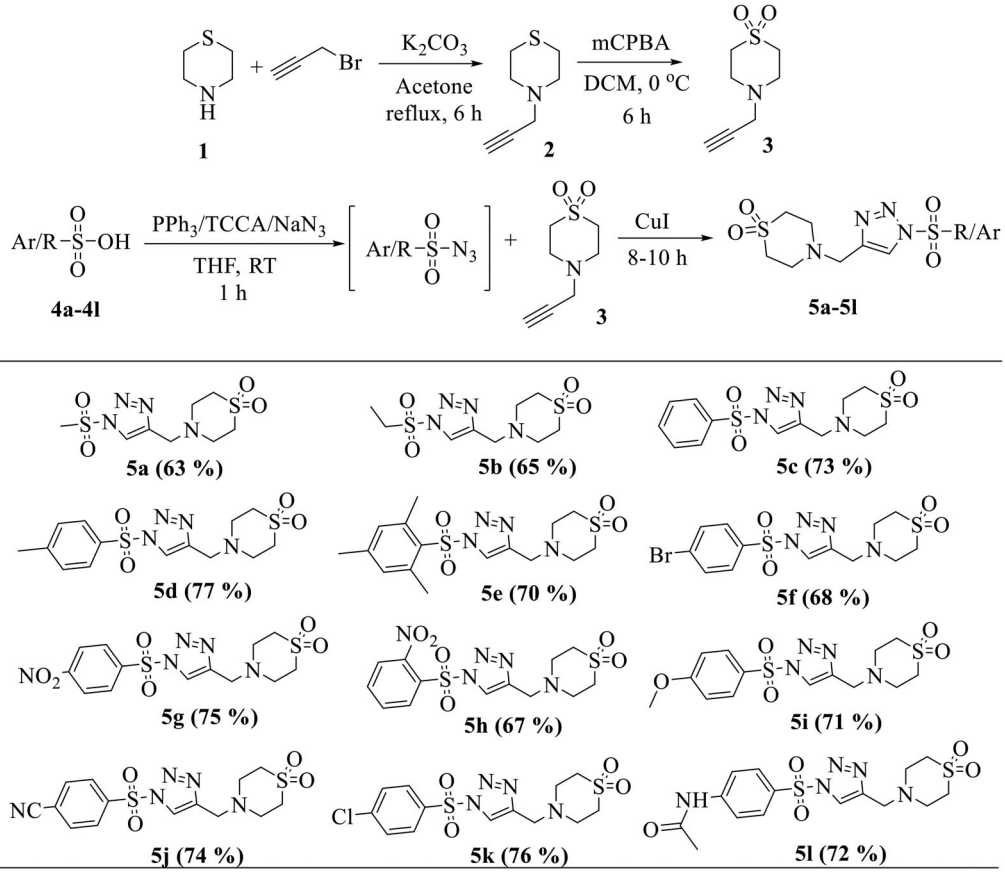


Scheme 1. One pot synthesis of sulfonyl-1*H*-1,2,3-triazolyl-thiomorpholine 1,1-dioxide.



Scheme 2. Synthesis of 1,2,3-triazole derivatives **5a-5l**.[a]
[a]The isolated yields are given as percentages.

the applications of previously developed Sharpless[13] and Batool methodologies (Scheme 1).[14]

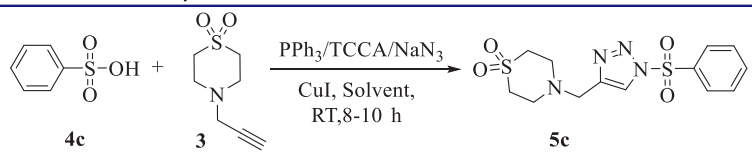
Results and discussion

The synthetic procedure adopted to obtain the targeted compounds is shown in Scheme 2. The 1,4-disubstituted-1,2,3-triazole derivatives were synthesized in a one-pot reaction, starting from sulfonic acid, 4-(prop-2-yn-1-yl)thiomorpholine 1,1-dioxide and sodium azide via an *in situ* generated sulfonylazide. 4-(Prop-2-yn-1-yl)thiomorpholine 1,1-dioxide (**3**) was synthesized by using previously reported method.[5g] One pot synthesis of 1,2,3-triazole was first tested on 4-(Prop-2-yn-1-yl)thiomorpholine 1,1-dioxide (**3**) and phenylsulfonic acid (**4c**) as model substrates in order to find optimal reaction conditions (Table 1). Our initial investigation began with the [3 + 2] cycloaddition of *in situ* generated phenylsulfonylazide from phenylsulfonic acid (**4c**), alkyne (**3**), PPh_3/TCCA/NaN_3, CuI, and solvent. After several trials (Table 1, entries **1–4**), the combination of 10 mol% of CuI and 4/1.5/2.5 molar ratio of PPh_3/TCCA/NaN_3 in the presence of THF at room temperature was found as suitable reaction condition for the synthesis of desired 4-((1-(phenylsulfonyl)-1H-1,2,3-triazol-4-yl)methyl)thiomorpholine 1,1-dioxide (**5c**) in good yield. Replacing the THF by other solvents such as CH_2Cl_2, $CHCl_3$, CH_3CN, and 1,4-dioxane decreased product yields (Table 1, entries **5–8**).

Using the above optimized conditions, we then extended our approach to synthesize several sulfonyl-1,2,3-trazoles and the results are shown in Scheme 2. It has been found that all the sulfonic acid used in the present approach were compatible to give the targeted sulfonyl-1,2,3-traizoles in good yields.

The structures of the newly synthesized compounds (**5a–5l**) were confirmed by ^{1}H NMR, ^{13}C NMR, ESI-MS, and elemental (CHN) analysis data. All the spectral and analytical data of the synthesized compounds were in full agreement with the proposed structures and also discussed for a representative compound **5a**. From the ^{1}H-NMR spectrum, the presence of the signals that appeared at δ 7.70 (s, 1H, triazole), δ 3.96 (s, 2H, N-CH_2-triazole), δ 3.32 (s, 3H, CH_3), δ 3.24–3.16 (m, 4H, 2SO_2-CH_2), δ 2.99–2.91 (m, 4H,

Table 1. Investigation of the reaction conditions for the synthesis of 1,2,3-triazole[a].



4c 3 5c

Entry	$PPh_3/TCCA/NaN_3$ molar ratio	Solvent	% Yield [b]
1	2/1/2	THF	16
2	3/1/2.5	THF	35
3	**4/1.5/2.5**	**THF**	**72**
4	5/2/3	THF	74
5	4/1.5/2.5	CH_2Cl_2	54
6	4/1.5/2.5	$CHCl_3$	58
7	4/1.5/2.5	CH_3CN	61
8	4/1.5/2.5	1,4-dioxane	63

[a]Reactions were performed with **4c** (2 mmol), **3** (2 mmol), CuI (10 mol%) and solvent (15 mL) for 8h. [b]Isolated yield

2 N-CH_2) confirmed the presence of required protons. From the ^{13}C-NMR, the presence of carbon signals at 131.35, 129.55 ppm (2C, triazole), 52.11 ppm (2C, 2SO_2-CH_2), 49.08 ppm (N-CH_2-tri), 48.68 ppm (2C, 2N-CH_2),40.07 ppm (SO_2-CH_3) confirmed the presence of characteristic carbon signals. The IR spectrum of a representative compound **5a** showed absorption bands in the region 3143, 1597, 1503, and 13,811,371 cm^{-1}, which were recognized to = C-H, C = N, C = C, and (SO_2) stretching vibrations. The presence of [M + H] ion peak at *m/z* 295 in ESI-Mass spectra and the elemental analysis (CHN) data (C, 32.57; H, 4.71; N, 18.95) confirmed the molecular formula ($C_8H_{14}N_4O_4S_2$) of compound **5a**.

Antibacterial activity

All the synthesized compounds were screened for their *in vitro* antibacterial activity against gram-positive (G+) bacterial strains was evaluated by the standard broth microdilution technique by using streptomycin as positive control.[15] The minimum inhibitory concentrations (MICs) for all the synthesized compounds were reported in μg/mL. The results of the antibacterial activity screening revealed that compound N-(4-((4-((1,1-dioxidothiomorpholino)methyl)-1*H*-1,2,3-triazol-1-yl)sulfonyl)phenyl)acetamide (**5l**) showed excellent inhibition against all the tested bacterial strains with MICs ranging from 1.56 ± 0.23 to 6.25 ± 0.52 μg/mL, respectively. Similarly, compound 4-((1-(mesitylsulfonyl)-1H-1,2,3-triazol-4-yl)methyl)thiomorpholine 1,1-dioxide (**5e**) showed excellent inhibition against *B. subtilis* and *S. aureus* with MIC values 3.12 ± 0.54 and 6.25 ± 0.38 μg/mL, and good inhibition against *S. epidermidis* with MIC value 12.5 ± 0.56 μg/mL, respectively. Compound 4-((1-((2-nitrophenyl)sulfonyl)-1H-1,2,3-triazol-4-yl)methyl)thiomorpholine 1,1-dioxide (**5j**) has shown good inhibition against all the tested bacterial strains with MICs ranging from 6.25 ± 0.39 to 12.5 ± 0.83 μg/mL, while the rest of the compounds have shown modest activity against all the tested strains with MIC values ranging from 12.5 ± 0.29 to 50 ± 1.38 μg/mL.

Antioxidant activity

All the synthesized compounds **5a–5l** were screened for free radical scavenging activity in terms of hydrogen donating or radical scavenging ability by 2,2-diphenyl-1- picrylhydrazyl (DPPH) method.[16] Methanol (95%), DPPH solution, and standard compounds (Troloxand ascorbic acid) were used as blank, control, and reference, respectively.

The examination of free radical scavenging ability of the synthesized compounds **5a–5l** results showed that compounds (**5j**, **5k**, and **5l**) have exhibited excellent antioxidant activity with IC_{50} values ranging from 6.38 ± 0.16 to 9.38 ± 0.52 µM. These results on comparison with the standard Trolox with IC_{50} value of 11.73 ± 0.89 µM found to be active by ≈1.84 fold for N-(4-((4-((1,1-dioxidothiomorpholino)methyl)-1*H*-1,2,3-triazol-1-yl) sulfonyl)phenyl)acetamide (**5l**), 1.44 fold for 4-((1-((2-nitrophenyl)sulfonyl)-1H-1,2,3-triazol-4-yl)methyl)thiomorpholine 1,1-dioxide (**5j**), and 1.25 fold for 4-((4-((1,1-dioxidothiomorpholino)methyl)-1H-1,2,3-triazol-1-yl)sulfonyl) benzonitrile (**5k**). The compounds **5g** and **5h** have shown good scavenging ability with IC_{50} values 17.84 ± 0.66 and 19.41 ± 0.59 µM, respectively. Remaining compounds have shown moderate to weak scavenging ability/capacity with IC_{50} values ranging from 23.13 ± 0.93 to 68.44 ± 1.09 µM. It is to point out that all the potent analogues which contain electron-withdrawing substituents like amido, cyano, chloro, and nitrophenyl sulfonyl groups on the triazole ring exhibited good to excellent antioxidant activity. The results of the antibacterial and antioxidant activities are presented in Table S1 (Supplemental materials).

Conclusion

In conclusion, we extended the applications of Sharpless and Batool Akhlaghinia methodologies for the synthesis of sulfonyl-1*H*-1,2,3-triazolyl-thiomorpholine 1,1-dioxide derivatives in one-pot using 4-(prop-2-yn-1-yl)thiomorpholine 1,1-dioxide and commercially available sulfonic acids via an *in situ* generated sulfonylazides. All the compounds screened for their *in vitro* antibacterial activity against three gram-positive bacterial strains and compounds **5l**, **5e**, and **5j**

showed a potent antibacterial activity against the bacterial strains. In addition, the compounds **5j**, **5k**, and **5l** have shown very good antioxidant activity when compared with the standard drug. These results suggest that the synthesized compounds might be useful for the optimization and development of new antibacterial agents for the treatment of bacterial infections.

Experimental

All the reactants were purchased from the Aldrich Chemical Company. All the reagents and solvents were purchased from SD Fine Chemicals limited and used without further purification. Thin-layer chromatography (TLC) was performed using Merck silica gel 60F254 precoated plates (0.25 mm), and silica gel (particle size 60–120 mesh) was used for column chromatography. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker (operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C). Mass spectra were recorded on a Jeol JMC-300 spectrometer (ESI, 70 eV). IR spectra were recorded on a Perkin Elmer BX series FT-IR spectrometer in KBr pellets. Elemental analyses were performed on Carlo Erba 106 and PerkinElmer model 240 analyzers. Melting points were determined using a Cintex apparatus and are uncorrected. The Supplemental materials contains sample ^{1}H and ^{13}C NMR and mass spectra of the products 5 (Figures S1–S35).

Synthesis of 4-(prop-2-yn-1-yl)thiomorpholine 1,1-dioxide (3)[5g]

To a stirred solution of 4-(prop-2-yn-1-yl)thiomorpholine (3 g, 0.021 mol) in dichloromethane (50 mL) was added *m*-CPBA (10.9 g, 0.0638 mol) at 0 °C. The reaction mixture was stirred at room temperature for 6 h. After completion of the reaction, the solvent was removed under reduced pressure to afford the crude compound. The crude product was partitioned between ethyl acetate and aqueous $NaHCO_3$ solution. Then, the organic layer was separated, washed with brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to afford 71% of 4-(prop-2-yn-1-yl)thiomorpholine 1,1-dioxide (**3**).

General procedure for the synthesis of sulfonyl-1H-1,2,3-triazolyl-thiomorpholine 1,1-dioxide derivatives (5a-5l)

To a 50 mL round bottom flask, trichloroisocyanuric acid (TCCA) (1.5 mmol) and PPh_3 (4 mmol) in THF (15 mL) were added and allowed to stir at 0–5 °C for 15 min. Then, the sulfonic acid (**4**) (2 mmol), and NaN_3 (2.5 mmol) were introduced into the resulting solution and stirring was continued at room temperature for 30–45 min. Later, the 4-(prop-2-yn-1-yl)thiomorpholine 1,1-dioxide (**3**) (2 mmol) and CuI (10 mmol%) and the resulting reaction mixture was stirred at room temperature for further 8 to 10 h. After the completion as shown by TLC, the reaction mixture was carefully poured into ice water (30 mL). The resulting solid was filtered, washed with excess of water and dried under reduced pressure. Finally, the crude product obtained was purified by column chromatography (eluent ethyl acetate–hexane, 2:3) to afford the pure desired 1,2,3-triazole derivatives in good yields.

4-((1-(Methylsulfonyl)-1H-1,2,3-triazol-4-yl)methyl)thiomorpholine 1,1-dioxide (5a)

Pale yellow solid; Mp: 127–129 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.70 (s, 1H, triazole), 3.96 (s, 2H, N-CH_2), 3.32 (s, 3H, CH_3), 3.24–3.16 (m, 4H, 2SO_2-CH_2), 2.99–2.91 (m, 4H, 2N-CH_2). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 131.35, 129.55, 52.11(2C, SO_2-CH_2), 49.08 (C, N-CH_2), 48.68 (2C, N-CH_2), 40.07 (C, SO_2-CH_3); IR (KBr, cm^{-1}) ν: 3143 (C-H, triazole), 1597 (C = N), 1503 (C = C), 1381, 1371 (SO_2), 1281, 1116, 1081 (SO_2); MS (ESI) *m/z*: 295 [M + H]; Anal. Calcd for $C_8H_{14}N_4O_4S_2$: C, 32.64; H, 4.79; N, 19.03. Found: C, 32.57; H, 4.71; N, 18.95.

4-((1-(Ethylsulfonyl)-1H-1,2,3-triazol-4-yl)methyl)thiomorpholine 1,1-dioxide (5 b)

Pale yellow solid; Mp: 130–132 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.75 (s, 1H, triazole), 3.97 (s, 2H, N-CH_2-tri), 3.36 (q, 3H, J = 2.2 Hz CH_3), 3.24 (t, 4H, J = 4.0 Hz, 2SO_2-CH_2), 2.95 (t, 4H, J = 4.0 Hz, 2N-CH_2), 1.62 (t, 3H, J = 4.0 Hz, CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 133.35, 128.31, 52.13 (2 C, SO_2-CH_2), 49.34 (C, N-CH_2), 48.23(2 C, N-CH_2), 41.01(C, SO_2-CH_2), 10.85 (C, C-CH_3); MS (ESI) *m/z*: 309 [M + H]; Anal. Calcd for $C_9H_{16}N_4O_4S_2$: C, 35.05; H, 5.23; N, 18.17. Found: C, 35.01; H, 5.29; N, 18.12.

4-((1-(Phenylsulfonyl)-1H-1,2,3-triazol-4-yl)methyl)thiomorpholine 1,1-dioxide (5c)

Yellow solid; Mp: 148–150 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.02 (s, 1H, triazole), 7.72 (d, 2H, J = 8.0 Hz, Ar-H), 7.58-7.48 (m, 1H, Ar-H), 7.40–7.33 (m, 2H, Ar-H), 3.96 (s, 2H, N-CH_2-tri), 3.23 (t, 4H, J = 4.0 Hz, 2SO_2-CH_2), 2.95 (t, 4H, J = 4.0 Hz, 2N-CH_2).^{13}C-NMR (100 MHz, $CDCl_3$) δ:138.65, 136.86, 135.05, 129.57, 128.65, 127.90, 52.61 (2C, SO_2-CH_2), 49.53 (C, N-CH_2), 48.61 (2C, N-CH_2); MS (ESI) *m/z*: 357 [M + H]; Anal. Calcd for $C_{13}H_{16}N_4O_4S_2$: C, 43.81; H, 4.52; N, 15.72. Found: C, 43.77; H, 4.48; N, 15.66.

4-((1-Tosyl-1H-1,2,3-triazol-4-yl)methyl)thiomorpholine 1,1-dioxide (5d)

Yellow solid; Mp: 154–156 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.99 (s, 1H, triazole), 7.82 (d, 2H, J = 8.0 Hz, Ar-H), 7.56–7.47 (m, 2H, Ar-H), 3.97 (s, 2H, N-CH_2), 3.21–3.10 (m, 4H, 2SO_2-CH_2), 2.94–2.82 (m, 4H, 2N-CH_2), 2.41 (s, 3H, Ar-CH_3).^{13}C-NMR (100 MHz, $CDCl_3$) δ: 141.63, 137.56, 136.35, 133.65, 132.68, 128.70, 52.70 (2C, SO_2-CH_2), 49.43(C, N-CH_2), 48.98(2C, N-CH_2), 21.61 (2C, Ar-CH_3); MS (ESI) *m/z*: 371 [M + H]; Anal. Calcd for $C_{14}H_{18}N_4O_4S_2$: C, 45.39; H, 4.90; N, 15.12. Found: C, 45.43; H, 4.95; N, 15.07.

4-((1-(Mesitylsulfonyl)-1H-1,2,3-triazol-4-yl)methyl)thiomorpholine 1,1-dioxide (5e)

White solid; Mp: 181–183 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.86 (s, 1H, triazole), 7.04 (s, 2H, Ar-H), 3.91 (s, 2H, N-CH_2), 3.22 (t, 4H, $J = 4.0$ Hz, 2SO_2-CH_2), 2.95 (t, 4H, $J = 4.0$ Hz, 2N-CH_2), 2.65 (s, 6H, 2Ar-CH_3), 2.32 (s, 3H, Ar-CH_3).^{13}C-NMR (100 MHz, $CDCl_3$) δ: 142.80, 137.50, 134.88, 131.86, 130.03, 127.29, 52.55 (2C, SO_2-CH_2), 49.53 (C, N-CH_2), 48.33 (2C, N-CH_2), 22.29 (2C, Ar-CH_3), 21.69 (C, Ar-CH_3); MS (ESI) *m/z*: 399 [M + H]; Anal. Calcd for $C_{16}H_{22}N_4O_4S_2$: C, 48.22; H, 5.56; N, 14.06. Found: C, 48.30; H, 5.59; N, 14.00.

4-((1-((4-Methoxyphenyl)sulfonyl)-1H-1,2,3-triazol-4-yl)methyl)thiomorpholine 1,1-dioxide (5f)

Pale red solid; Mp: 163–165 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.06 (s, 1H, triazole), 7.85 (d, 2H, $J = 8.0$ Hz, Ar-H), 7.09 (d, 2H, $J = 8.0$ Hz, Ar-H), 3.98 (s, 2H, N-CH_2-tri), 3.84 (s, 3H, O-CH_3), 3.19 (t, 4H, $J = 4.0$ Hz, 2SO_2-CH_2), 2.90 (m, 4H, $J = 4.0$ Hz, 2 N-CH_2). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 163.42, 136.67, 131.63, 131.27, 130.03, 118.47, 57.00 (C, O-CH_3), 52.07 (2C, SO_2-CH_2), 49.34 (C, N-CH_2), 48.98 (2C, N-CH_2); MS (ESI) *m/z*: 387 [M + H]; Anal. Calcd for $C_{14}H_{18}N_4O_5S_2$: C, 43.51; H, 4.69; N, 14.50. Found: C, 43.58; H, 4.63; N, 14.44.

4-((1-((4-Chlorophenyl)sulfonyl)-1H-1,2,3-triazol-4-yl)methyl)thiomorpholine 1,1-dioxide (5g)

Pale yellow solid; Mp: 159–161 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.12 (s, 1H, triazole), 7.93 (d, 2H, $J = 8.8$ Hz, Ar-H),7.53 (d, 2H, $J = 8.8$ Hz, Ar-H), 3.97 (s, 2H, N-CH_2-tri), 3.26 (t, 4H, $J = 4.0$ Hz, 2SO_2-CH_2), 2.95 (t, 4H, $J = 4.0$ Hz, 2 N-CH_2). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 142.66, 138.47, 136.40, 134.56, 130.04, 129.94, 52.58 (2C, SO_2-CH_2), 49.49 (C, N-CH_2), 48.61 (2C, N-CH_2); MS (ESI) *m/z*: 391 [M + H]; Anal. Calcd for $C_{13}H_{15}ClN_4O_4S_2$: C, 39.95; H, 3.87; N, 14.33. Found: C, 39.90; H, 3.82; N, 14.27.

4-((1-((4-Bromophenyl)sulfonyl)-1H-1,2,3-triazol-4-yl)methyl)thiomorpholine 1,1-dioxide (5h)

Yellow solid; Mp: 168–170 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.00 (s, 1H, triazole), 7.85–7.78 (m, 2H, Ar-H), 7.69–7.61 (m, 2H, Ar-H), 3.97 (s, 2H, N-CH_2), 3.25 (t, 4H, $J = 4.0$ Hz, 2SO_2-CH_2), 2.97 (t, 4H, $J = 4.0$ Hz, 2N-CH_2).^{13}C-NMR (100 MHz, $CDCl_3$) δ: 142.22, 138.28, 136.23, 134.50, 130.17, 128.27, 52.18 (2C, SO_2-CH_2), 49.69 (C, N-CH_2), 48.13 (2C, N-CH_2); MS (ESI) *m/z*: 434 [M + H] & 436 [M + 3H]; Anal. Calcd for $C_{13}H_{15}BrN_4O_4S_2$: C, 35.87; H, 3.47; N, 12.87. Found: C, 35.81; H, 3.42; N, 12.82.

4-((1-((4-Nitrophenyl)sulfonyl)-1H-1,2,3-triazol-4-yl)methyl)thiomorpholine 1,1-dioxide (5i)

Yellow solid; Mp: 177–179 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.48 (d, 2H, $J = 8.0$ Hz, Ar-H), 8.28 (d, 2H, $J = 8.0$ Hz, Ar-H), 8.16 (s, 1H, triazole),4.02 (s, 2H, N-CH_2-tri), 3.33 (t, 4H, $J = 4.0$ Hz, 2SO_2-CH_2), 3.00 (t, 4H, $J = 4.0$ Hz, 2N-CH_2). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 147.02, 142.84, 135.91, 130.04, 127.23, 123.02, 52.21 (2C, SO_2-CH_2), 49.23 (C, N-CH_2), 48.61 (2C, N-CH_2); MS (ESI) *m/z*: 402 [M + H]; Anal. Calcd for $C_{13}H_{15}N_5O_6S_2$: C, 38.90; H, 3.77; N, 17.45. Found: C, 38.85; H, 3.72; N, 17.52.

4-((1-((2-Nitrophenyl)sulfonyl)-1H-1,2,3-triazol-4-yl)methyl)thiomorpholine 1,1-dioxide (5j)

Yellow solid; Mp: 175–177 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.40–8.31 (m, 1H, Ar-H), 8.21–8.17 (m, 1H, Ar-H), 8.15 (s, 1H, triazole), 7.99–7.85 (m, 3H), 3.99 (s, 2H, N–CH_2), 3.38–3.26 (m, 4H, 2SO_2-CH_2), 3.00–2.87 (m, 4H, 2N-CH_2).^{13}C-NMR (100 MHz, $CDCl_3$) δ: 148.78, 138.24, 134.79, 134.62, 131.99, 130.22, 127.69, 125.08, 52.51 (2C, SO_2-CH_2), 49.28 (C, N-CH_2), 48.79 (2C, N-CH_2); MS (ESI) *m/z*: 402 [M + H]; Anal. Calcd for $C_{13}H_{15}N_5O_6S_2$: C, 38.90; H, 3.77; N, 17.45. Found: C, 38.82; H, 3.79; N, 17.50.

4-((4-((1,1-Dioxidothiomorpholino)methyl)-1H-1,2,3-triazol-1-yl)sulfonyl)benzonitrile (5k)

Pale red solid; Mp: 166–168 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.11–8.03 (m, 3H, Ar-H & triazole), 7.86–7.80 (m, 2H, Ar-H), 3.99 (s, 2H, N–CH_2), 3.29–3.24 (m, 4H, 2SO_2-CH_2), 2.98–2.89 (m, 4H, 2N-CH_2).^{13}C-NMR (100 MHz, $CDCl_3$) δ: 145.01, 135.31, 132.33, 128.25, 126.69, 119.98, 118.01, 52.33 (2C, SO_2-CH_2), 49.65 (C, N-CH_2), 48.92 (2C, N-CH_2); MS (ESI) *m/z*: 382 [M + H]; Anal. Calcd for $C_{14}H_{15}N_5O_4S_2$: C, 44.08; H, 3.96; N, 18.36. Found: C, 44.11; H, 3.89; N, 18.32.

N-(4-((4-((1,1-dioxidothiomorpholino)methyl)-1H-1,2,3-triazol-1-yl)sulfonyl)phenyl) acetamide (5l)

Pale yellow solid; Mp: 199–201 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.07 (s, 1H, triazole), 7.92–7.83 (m, 2H, Ar-H),7.79–7.70 (m, 2H, Ar-H),7.60 (br, 1H, NH), 3.99 (s, 2H, N–CH_2), 3.25 (t, 4H, $J = 4.0$ Hz, 2SO_2-CH_2), 2.98–2.89 (t, 4H, $J = 4.0$ Hz, 2N-CH_2), 2.29 (s, 3H, CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 169.42, 147.54, 136.03, 135.93, 130.01, 126.97, 120.29, 52.51 (2C, SO_2-CH_2), 49.43 (C, N-CH_2), 48.98 (2C, N-CH_2), 23.36(C, CO-CH_3); MS (ESI) *m/z*: 414 [M + H]; Anal. Calcd for $C_{15}H_{19}N_5O_5S_2$: C, 43.57; H, 4.63; N, 16.94. Found: C, 43.65; H, 4.58; N, 16.88.

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Disclosure statement

No potential conflict of interest was reported by the authors.

ORCID

Sirassu Narsimha http://orcid.org/0000-0002-1844-2937

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