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Original article

Synthesis, characterization and antimicrobial studies of 2-(4-methoxy-phenyl)-5-methyl-4-(2-arylsulfanyl-ethyl)-2,4-dihydro-[1,2,4] triazolo-3-ones and their corresponding sulfones

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ABSTRACT

In the present investigation, a series of novel 2-(4-methoxy-phenyl)-5-methyl-4-(2-arylsulfanyl-ethyl)-2,4-dihydro-[1,2,4] triazolo-3-ones and their corresponding sulfones were prepared with the objective of developing better antimicrobial agents. The chemical structures of the newly synthesized compounds were characterized by spectral (IR, ^{1}H NMR, ^{13}C NMR and LCMS) methods. The newly synthesized compounds (**4a**–**i**) and (**5a**–**e**, **5h**) were screened for their antimicrobial activity against *Bacillus subtilis*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Escherichia coli* and *Pseudomonas aeruginosa*. The antifungal activity was tested against *Rhizopus oryzae*, *Aspergillus niger*, *Aspergillus flavus*, *Candida albicans* and *Saccharomyces cerevisiae*. Among all the compounds synthesized, compounds **4d** and **5b** exhibited significant antibacterial activity.

1. Introduction

The development of drug resistance to clinically used anti-infective agents has increased the demand for discovery of new chemical scaffolds with antimicrobial activity. In addition increase in immuno compromised patients and hospital acquired infections has necessitated the exploration of new biological targets and discovery of effective antibacterial and antifungal agents.

The 1,2,4-triazoles and their derivatives were found to be associated with various biological activities such as antibacterial [1–7], antifungal [4–8], antitubercular [9–11], analgesic [12,13], anti-inflammatory [13–15], anticancer [16,17], anticonvulsant [18,19], antiviral [20,21], insecticidal [22], antidepressant [23] and central nervous system (CNS) [24] activities. Also the 1,2,4-triazole ring with sulfones and thioethers show a wide range of biological activities such as antibacterial and antifungal [25], antihypertensive [26], analgesic, anti-inflammatory [27], and pesticidal [28,29]. 1,3,4-oxadiazoles exhibit wide spectrum of biological activities such as HIV, antibacterial and antifungal [2,30], analgesic [31], anti-malarial [32] and anti-inflammatory [33–35] activities.

Several 1,2,4-triazole containing compounds are used as drugs (Fig. 1); for instance, fluconazole is used as an antimicrobial drug [36], while vorozole, letrozole and anastrozole are non steroidal drugs used for the treatment of cancer [37]. Loreclezole is used as an anticonvulsant [38] where as itraconazole is used as an anti-fungal agent.

Keeping in mind the above facts, we were interested to synthesize some more 1,2,4-triazol containing thioethers and their corresponding sulfones.

2. Chemistry

Synthetic pathway for the preparation of title compounds is depicted in Scheme 1. The oxadiazolinone (**1**) was synthesized as reported in the literature [39]. The key intermediate 4-(2-hydroxy-ethyl)-2-(4-methoxy-phenyl)-5-methyl-2,4-dihydro-3H-1,2,4-triazol-3-one (**2**) was prepared from one pot ring conversion of oxadiazolinone (**1**). The hydroxyethyl derivative (**2**) was utilized as a precursor to introduce various heterocycles. 5-(4-chloro-phenyl) [1,3,4] oxadiazol-2-thiol (**3a**) was synthesized according to a previously reported method [40].

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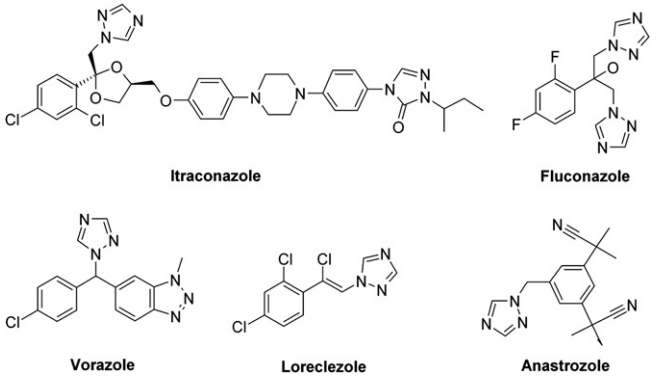


Fig. 1. Drugs containing 1,2,4-triazole moiety.

The reaction of hydroxyethyl compound (**2**) with methane sulfonyl chloride afforded the mesylate (**3**). This on further reaction with different thiols gave thethioethers (**4a**–**i**) in good yields. These thioethers on oxidation with *m*-CPBA afforded the corresponding sulfones (**5a**–**e**, **5h**) in excellent yields.

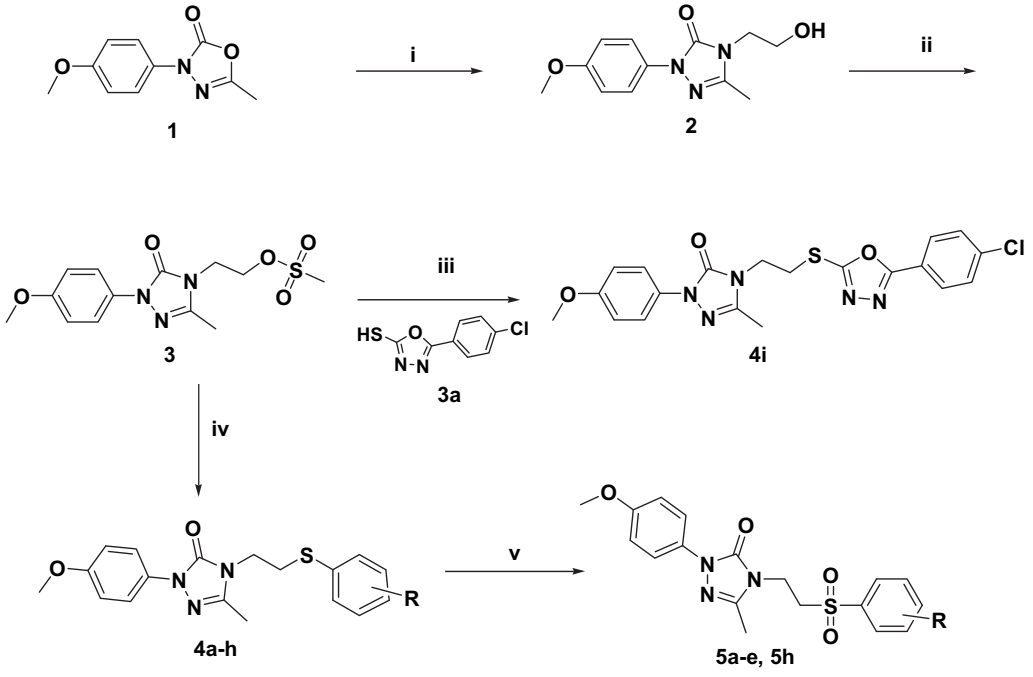
3. Biological activity

The *in vitro* antimicrobial activity was carried out by disc diffusion method in dimethylformamide (DMF) as solvent [41,42]. The newly synthesized compounds were screened for antibacterial activity against *Bacillus subtilis*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Escherichia coli* and *Pseudomonas aeruginosa*. The antifungal activity was tested against *Rhizopus oryzae*, *Aspergillus niger, Aspergillus flavus*, *Candida albicans*, and *Saccharomyces cerevisiae* The MIC was determined by using two-fold serial dilution method with 64-well microtest plates. Streptomycin and Penicillin were used for antibacterial activity as reference standards and Ampotericin-B as a reference standard with good antifungal activity.

For determining both antibacterial and antifungal activities, the synthesized compounds and the control drugs were dissolved in redistilled DMF. Further dilutions were made at the required concentrations of 300, 150, 75, 37.5, 18.75, 9.75, 6.25, 3.125 and 1.56 μg/mL respectively. In order to ensure that the solvent had no effect on bacterial growth, a control test was performed containing broth supplemented with only DMF at the same dilution as used in the experiment. The MIC values were obtained from the lowest concentration of the test compound, where the tubes remain clear, indicating that the bacterial growth was completely inhibited at this concentration.

The results of antimicrobial screening revealed that both thioethers (**4a**–**i**) and their corresponding sulfones (**5a**–**e**, **5h**) displayed better antibacterial activity compared with their antifungal activities. The results of antibacterial activity are given in Table 1. From the results it was observed that the compound **4d** (R = 3-CF_3) showed good inhibition against *S. aureus* and *E. coli*. The compound **5b** (R = 3-F) had moderate activity against *S. aureus* and *E. coli* (Fig. 2).

The compound with fluoro substitution **4a** (R = 2-F) exhibited significant activity against *S. aureus,* where as the compound with methoxy group **4f** (R = 4-OCH_3) showed moderate activity against *B. subtilis* and *E. coli*. Among all the newly synthesized compounds, **4c**, **4e**, **4g**, **4h**, **4i**, **5a** and **5c** showed poor activity.

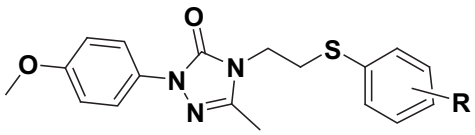


R = a) 2-F, b) 3-F, c) 4-F, d) 3-CF_3,e) 4-Br, f) 3-OCH_3, g) 4-NH_2, h) H

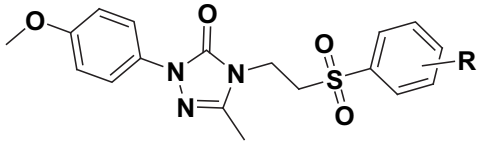
i) $NH_2CH_2CH_2OH$, reflux, 16 h, ii) MsCl, pyridine, 0°C to rt, 4 h, iii) Cs_2CO_3, CuI, DMF,100°C, 10 h
iv) R-PhSH, Cs_2CO_3, CuI, DMF,100°C, 6-9 h, v) *m*-CPBA, DCM, 0-5°C, 30 min

Scheme 1. Synthesis of 1,2,4-triazole thioethers and their corresponding sulfones.

Table 1
Antibacterial activities of the compounds (**4a**–**h**) and (**5a**–**e**).



4a-h



5a-e, 5h

R	Compounds	*B. subtilis*	*S. aureus*	*S. epidermidis*	*E. coli*	*P. aeruginosa*
2-F	**4a**	37.5	**9.75**	150	75	37.5
3-F	**4b**	150	37.5	75	150	37.5
4-F	**4c**	150	75	75	150	75
3-CF_3	**4d**	150	**9.75**	150	**9.75**	75
4-Br	**4e**	75	150	150	150	75
3-OCH_3	**4f**	**18.75**	75	150	**18.75**	75
4-NH_2	**4g**	75	75	75	150	150
H	**4h**	75	75	37.5	37.5	75
	4i	150	75	150	150	150
2-F	**5a**	150	37.5	75	150	37.5
3-F	**5b**	75	**18.75**	37.5	**9.375**	150
4-F	**5c**	75	75	37.5	37.5	75
3-CF_3	**5d**	37.5	**18.75**	75	37.5	**18.75**
4-Br	**5e**	75	**9.375**	150	150	150
H	**5h**	150	37.5	75	150	75
	Streptomycin	**6.25**	**1.56**	**1.562**	**3.125**	**3.125**
	Penicillin	**1.526**	**6.25**	**3.125**	**7.81**	**12.5**

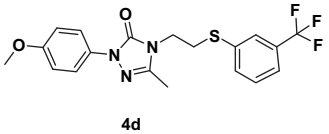
(MIC, μg/mL) minimum inhibitory concentration.

The results of antifungal activity are depicted in Table 2 and compared with the standard Amphotericin-B. Almost all the newly synthesized compounds showed poor activity against all types of fungal strains. Thus thioethers (**4a**–**i**) and corresponding sulfones (**5a**–**e**, **5h**) of 1,2,4-triazole exhibited good antibacterial activity. Further studies are in progress to develop a novel series of antibacterial agents.

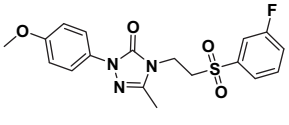
4. Results and discussion

All new compounds were characterized by their spectral data. The IR spectra of thioethers (**4a**–**i**) showed bands at 1696 cm^{-1} (C=O of triazolinone) 1535 cm^{-1} (C=N). The ^1H NMR spectrum (**4a**) showed a singlet at δ 2.25 ppm for the $-CH_3$ protons of triazolinone ring. The two distorted triplet at 3.85 and 3.33 ppm were assigned to the methylene protons. The signals at 6.93 and 7.79 were assigned to the aromatic protons. The structure of these compounds was further confirmed by its mass spectral analysis. LCMS of a typical compound (**4e**) showed the molecular ion peaks at 420 and 422 (1:1 isotopic peak for bromine) which agrees with the molecular weight of the compound.

The IR spectrum of sulfones (**5a**–**e**, **5h**) exhibited S=O stretching bands at 1329 (assym), and 1148 (sym) cm^{-1} where as the triazolinone C=O stretching observed at 1710 cm^{-1}. The ^1H NMR spectrum of sulfones showed the downfield shift of $-SO_2CH_2-$ protons when compared with thioether derivatives (**4a**–**i**). The ^1H NMR spectrum (**5a**) showed a singlet at δ 2.27 ppm for $-CH_3$ protons of triazolinone ring. The two methylene protons were merged and observed at δ 4.01ppm. The signals at 6.94 and 7.33–7.79 were assigned to the aromatic protons. The structures of these compounds were further confirmed by their mass spectral analysis. LCMS of a typical compound (**5a**) showed [M + 1] peak at 392.0 which agrees with the molecular weight of the compound.



4d



5b

Fig. 2. Most potent compounds among the newly synthesized compounds.

5. Conclusion

A series of novel thioethers (**4a**–**i**) and corresponding sulfones (**5a**–**e**, **5h**) were synthesized and characterized by NMR, mass

Table 2
Antifungal activities of the compounds (**4a**–**h**) and (**5a**–**e**).

R	Compounds	*R. oryzae*	*A. niger*	*A. flavus*	*C. albicans*	*S. cerevisiae*
2-F	**4a**	9.75	150	150	37.5	150
3-F	**4b**	37.5	150	150	150	150
4-F	**4c**	150	150	150	150	150
3-CF_3	**4d**	18.75	150	150	150	150
4-Br	**4e**	75	75	75	150	150
3-OCH_3	**4f**	37.5	37.5	75	150	150
4-NH_2	**4g**	37.5	37.5	75	150	150
H	**4h**	75	37.5	75	150	150
	4i	150	150	150	150	150
2-F	**5a**	18.75	37.5	75	150	150
3-F	**5b**	37.5	37.5	75	150	150
4-F	**5c**	75	37.5	75	150	150
3-CF_3	**5d**	75	37.5	75	150	150
4-Br	**5e**	37.5	37.5	75	150	150
H	**5h**	150	150	150	150	150
	Amphoterin-B	**1.562**	**1.56**	**6.25**	**6.25**	**6.25**

(MIC, μg/mL) minimum inhibitory concentration.

spectrometry and IR studies. The yields were found to be satisfactory. The newly synthesized compounds were screened for their antibacterial and antifungal activities. Among all the compounds **4d** ($R = 3\text{-}CF_3$) and **4a** ($R = 2\text{-}F$) exhibited good inhibition against *S. aureus* and *E. coli*. Most of the compounds showed better antibacterial activity, further optimization and development of this series is required for drug development.

6. Experimental

Melting points were determined in Buchi B-545 melting point apparatus and were presented without corrections. The IR spectra were recorded on a Nicolet 6700 FT-IR spectrometry using ATR-technique (ATR = Attenuated Total Reflectance). NMR spectra were recorded on Bruker (400 MHz) spectrometer instruments. ^{1}H NMR spectra were recorded in $CDCl_3$ and DMSO-d_6 using tetramethylsilane (TMS) as an internal reference. ^{13}C NMR spectra were recorded for approximately 0.05M solutions in DMSO-d_6 at 100 MHz with TMS as internal reference. Mass spectra were recorded on LC-MS-Agilent 1200 series. C, H, N and S analysis were carried out on an Elementor (Vario micro cube) instrument. All the above compounds were purified by flash column chromatography over silica gel (230–400 mesh).

The synthesis of 4-(2-hydroxy-ethyl)-2-(4-methoxy-phenyl)-5-methyl-2,4-dihydro-3H-1,2,4-triazol-3-one (**2**) and Methanesulfonic acid 2-[1-(4-methoxy-phenyl)-3-methyl-5-oxo-1,5-dihydro-[1,2,4] triazol-4yl]-ethyl ester (**3**) were carried out by reported methods [39]. Also 5-(4-chloro-phenyl) [1,3,4] oxadiazol-2-thiol (**3a**) was synthesized according to literature method [40].

6.1. General procedure to synthesize thioethers (*4a–i*)

A mixture of mesyl derivative (**3**) (2 mmol), substituted thiols (2.1 mmol), Cs_2CO_3 (4 mmol) and CuI (0.2 mmol) in DMF (4 mL) was stirred at 100 °C for 6–10 h. The progress of the reaction was monitored by TLC. After the completion of reaction, the mixture was cooled and diluted with water. The product was extracted with ethyl acetate (2 × 20 mL). The combined organic phase was washed with water (2 × 20 mL), brine (20 mL) and dried over sodium sulfate. The solvent was evaporated to afford the thioethers in moderate to good yields.

6.2. 4-[2-(2-Fluoro-phenylsulfanyl)-ethyl]-2-(4-methoxy-phenyl)-5-methyl-2,4-dihydro-[1,2,4] triazol-3-one (*4a*)

Purified by column chromatography (Petroleum ether/Ethyl acetate, 40/60); white solid; yield: 96%; mp 90.8–92.2 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.67 (d, 2H, $J = 9.12$ Hz, Ar–H), 7.57–7.54 (m, 1H, Ar–H), 7.25–7.13 (m, 3H, Ar–H), 6.98 (d, 2H, $J = 9.12$ Hz, Ar–H), 3.85 (t, 2H, $J = 6.8$ Hz, N–CH_2), 3.75 (s, 3H, O–CH_3), 3.35 (t, 2H, $J = 6.8$ Hz, S–CH_2), 2.24 (s, 3H, Ar–CH_3), ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.0, 156.4, 151.2, 144.5, 130.9, 130.2, 128.4, 125.1, 121.7, 119.6, 115.6, 114.11, 55.31, 40.7, 29.57, 11.38. MS: *m/z* 360.0 [M + 1]; Anal. Calcd for $C_{18}H_{18}FN_3O_2S$: C, 60.15; H, 5.05; N, 11.69; S, 8.9. Found: C, 59.98; H, 5.03; N, 11.70; S, 8.88.

6.3. 4-[2-(3-Fluoro-phenylsulfanyl)-ethyl]-2-(4-methoxy-phenyl)-5-methyl-2,4-dihydro-[1,2,4] triazol-3-one (*4b*)

Purified by column chromatography (Petroleum ether/Ethyl acetate, 40/60); off white solid; yield: 94%; mp 94.9–96 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.70 (d, 2H, $J = 9.08$ Hz, Ar–H), 7.35–7.28 (m, 2H, Ar–H), 7.21 (d, 1H, $J = 8.00$ Hz, Ar–H), 6.99 (d, 2H, $J = 9.08$ Hz, Ar–H), 6.98–6.95 (m, 2H, Ar–H), 3.86 (t, 2H, $J = 6.78$ Hz, N–CH_2), 3.76 (s, 3H, O–CH_3), 3.38 (t, 2H, $J = 6.78$ Hz, S–CH_2), 2.24 (s, 3H, Ar–CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.4, 156.4, 151.3, 144.5, 137.8, 130.9, 130.8, 123.6, 119.6, 114.2, 114.1, 112.7, 55.3, 40.5, 29.7, 11.4. MS: *m/z* 360.0 [M + 1]; Anal. Calcd for $C_{18}H_{18}FN_3O_2S$: C, 60.15; H, 5.05; N, 11.69; S, 8.9. Found: C, 60.08; H, 5.04; N, 11.67; S, 8.92.

6.4. 4-[2-(4-Fluoro-phenylsulfanyl)-ethyl]-2-(4-methoxy-phenyl)-5-methyl-2,4-dihydro-[1,2,4] triazol-3-one (*4c*)

Purified by column chromatography (Petroleum ether/Ethyl acetate, 40/60); white solid; yield: 94%; mp 97.8–99.3 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.68 (d, 2H, $J = 9.14$ Hz, Ar–H), 7.47–7.43 (m, 2H, Ar–H), 7.16–7.11 (m, 2H, Ar–H), 6.99 (d, 2H, $J = 9.14$ Hz, Ar–H), 3.82 (t, 2H, $J = 6.72$ Hz, N–CH_2), 3.75 (s, 3H, O–CH_3), 3.31 (t, 2H, $J = 6.72$ Hz, S–CH_2), 2.24 (s, 3H, Ar–CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.0, 156.4, 151.2, 144.5, 131.2, 131.0, 130.1, 119.5, 116.2, 114.1, 55.33, 40.83, 31.29, 11.49. MS: *m/z* 360.0 [M + 1]; Anal. Calcd for $C_{18}H_{18}FN_3O_2S$: C, 60.15; H, 5.05; N, 11.69; S, 8.9. Found: C, 60.05; H, 5.03; N, 11.71; S, 8.91.

6.5. 2-(4-Methoxy-phenyl)-5-methyl-4-[2-(3-trifluoromethyl-phenylsulfanyl)-ethyl]-2,4-dihydro-[1,2,4] triazol-3-one (*4d*)

Purified by column chromatography (Petroleum ether/Ethyl acetate, 45/55); off white solid; yield: 73%; mp 99.8–101.6 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.77–7.72 (m, 2H, Ar–H), 7.69 (d, 2H, $J = 9.08$ Hz, Ar–H), 7.53–7.46 (m, 2H, Ar–H), 6.99 (d, 2H, $J = 9.08$ Hz, Ar–H), 3.88 (t, 2H, $J = 6.78$ Hz, N–CH_2), 3.76 (s, 3H, O–CH_3), 3.46 (t, 2H, $J = 6.78$ Hz, S–CH_2), 2.25 (s, 3H, Ar–CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 156.8, 151.6, 144.9, 137.4, 132.1, 131.4, 130.5, 130.2, 125.6, 124.4, 122.9, 119.9, 114.5, 55.72, 41.05, 30.31, 11.81. MS: *m/z* 409.9 [M + 1]; Anal. Calcd for $C_{19}H_{18}F_3N_3O_2S$: C, 55.74; H, 4.43; N, 10.26; S, 7.83. Found: C, 55.69; H, 4.42; N, 10.30; S, 7.81.

6.6. 4-[2-(4-Bromo-phenylsulfanyl)-ethyl]-2-(4-methoxy-phenyl)-5-methyl-2,4-dihydro-[1,2,4] triazol-3-one (*4e*)

Purified by column chromatography (Petroleum ether/Ethyl acetate, 50/50); pale yellow solid; yield: 93%, mp 108.5–109.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (d, 2H, $J = 9.04$ Hz, Ar–H), 7.45 (d, 2H, $J = 8.56$ Hz, Ar–H), 7.34 (d, 2H, $J = 8.56$ Hz, Ar–H), 6.98 (d, 2H, $J = 9.04$ Hz, Ar–H), 3.84 (t, 2H, $J = 6.66$ Hz, N–CH_2), 3.75 (s, 3H, O–CH_3), 3.34 (t, 2H, $J = 6.66$ Hz, S–CH_2), 2.23 (s, 3H, Ar–CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 156.8, 151.6, 144.9, 134.9, 132.31, 131.3130.4, 120.03, 119.4, 114.5, 55.7, 41.1, 30.5, 11.87. MS: *m/z* 420 [M +] 422 [M + 2]; Anal. Calcd for $C_{18}H_{18}BrN_3O_2S$: C, 51.44; H, 4.32; N, 10.00; S, 7.63. Found: C, 51.54; H, 4.33; N, 9.98; S, 7.61.

6.7. 2-(4-Methoxy-phenyl)-4-[2-(3-Methoxy-phenylsulfanyl)-ethyl]-5-methyl-2,4-dihydro-[1,2,4] triazol-3-one (*4f*)

Purified by column chromatography (Petroleum ether/Ethyl acetate, 45/55); off white solid; yield: 90%; mp 74.6–75.9 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.69 (d, 2H, $J = 8.98$ Hz, Ar–H), 7.19 (m, 2H, Ar–H), 6.98 (d, 2H, $J = 8.98$ Hz, Ar–H), 6.95–6.93 (m, 2H, Ar–H), 6.72–6.70 (m, 1H, Ar–H), 3.84 (t, 2H, $J = 6.70$ Hz, N–CH_2), 3.75 (s, 3H, O–CH_3), 3.71 (s, 3H, O–CH_3), 3.33 (t, 2H, $J = 6.70$ Hz, S–CH_2), 2.23 (s, 3H, Ar–CH_3); ^{13}C NMR (100 MHz DMSO-d_6): δ 160.1, 156.8, 151.6, 145.0, 136.5, 131.4, 130.4, 120.4, 120.0, 114.5, 113.3, 112.3, 55.7, 55.5, 41.2, 30.2, 11.8. MS: *m/z* 372 [M + 1]; Anal. Calcd for $C_{19}H_{21}N_3O_3S$: C, 61.44; H, 5.70; N, 11.31; S, 8.63. Found: C, 61.37; H, 5.72; N, 11.34; S, 8.62.

*6.8. 4-[2-(4-Amino-phenylsulfanyl)-ethyl]-2-(4-methoxy-phenyl)-5-methyl-2,4-dihydro-[1,2,4] triazol-3-one (**4g**)*

Purified by column chromatography (Petroleum ether/Ethyl acetate, 30/70), Dark brown thick liquid; yield: 73%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.72 (d, 2H, J = 8.92 Hz, Ar–H), 7.15 (d, 2H, J = 8.34 Hz, Ar–H), 6.99 (d, 2H, J = 8.92 Hz, Ar–H), 6.52 (d, 2H, J = 8.34 Hz, Ar–H), 5.28 (s, 2H, Ar–NH_2), 3.76 (s, 3H, O–CH_3), 3.74 (t, 2H, J = 6.28 Hz, N–CH_2), 3.04 (t, 2H, J = 6.28 Hz, S–CH_2), 2.21 (s, 3H, Ar–CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 156.4, 151.26, 148.6, 144.6, 133.3, 131.0, 119.6, 117.5114.5, 114.1 55.3, 40.8, 33.4, 11.4. MS: m/z 357 [M + 1]; Anal. Calcd for $C_{18}H_{20}N_4O_2S$: C, 60.65; H, 5.66; N, 15.72; S, 9.00. Found: C, 60.73; H, 5.65; N, 15.70; S, 8.99.

*6.9. 4-(2-Phenylsulfanyl-ethyl)-2-(4-methoxy-phenyl)-5-methyl-2,4-dihydro-[1,2,4] triazol-3-one (**4h**)*

Purified by column chromatography (Petroleum ether/Ethyl acetate, 30/70), pale yellow solid; yield: 91%; mp 86.3–86.5 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.69 (d, 2H, J = 9.14 Hz, Ar–H), 7.41–7.37 (m, 2H, Ar–H), 7.31–7.27 (m, 2H, Ar–H), 7.18–7.14 (m, 1H, Ar–H), 6.98 (d, 2H, J = 9.14 Hz, Ar–H), 3.83 (t, 2H, J = 6.72 Hz, N–CH_2), 3.75 (s, 3H, O–CH_3), 3.32 (t, 2H, J = 6.72 Hz, S–CH_2), 2.21 (s, 3H, Ar–CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.1, 151.7, 143.5, 134.4, 131.0, 129.2, 129.1, 126.6, 120.4, 114.0, 55.4, 41.6, 31.5, 11.8. MS: m/z 342.2 [M + 1]; Anal. Calcd for C_{18}H19N3O_2S: C, 63.32; H, 5.61; N, 12.31; S, 9.39. Found: C, 63.53; H, 5.60; N, 12.30; S, 9.36.

*6.10. 4-{2-[5-(4-Chloro-phenyl)-[1,3,4] oxadiazol-2-yl-sulfanyl]-ethyl}-2-(4-methoxy-phenyl)-5-methyl-2,4-dihydro-[1,2,4] triazol-3-one (**4i**)*

Purified by recrystallisation (DCM/Methanol); light brown solid; yield: 68%; mp 181.9–183.2 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.91 (d, 2H, J = 9.00 Hz, Ar–H), 7.63–7.58 (m, 4H, Ar–H), 6.90 (d, 2H, J = 9.00 Hz, Ar–H), 4.09 (t, 2H, J = 6.20 Hz, N–CH_2), 3.73 (s, 3H, O–CH_3), 3.64 (t, 2H, J = 6.20 Hz, S–CH_2), 2.31 (s, 3H, Ar–CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.8, 163.8, 156.7, 151.6, 145.0, 137.1, 131.3, 129.9, 128.6, 122.1, 119.8, 114.4, 55.6, 40.5, 31.1, 11.96. MS: m/z 443 [M + 1]; Anal. Calcd for $C_{20}H_{18}ClN_5O_3S$: C, 54.15; H, 4.09; N, 15.7; S, 7.22. Found: C, 54.06; H, 4.10; N, 15.73; S, 7.24.

*6.11. General procedure to synthesize 4-[substituted-(benzenesulfonyl)-ethyl]-2-(4-methoxy-phenyl)-5-methyl-2,4-dihydro-[1,2,4] triazole-3-one (**5a**–**e**)*

To a solution of thioethers (**4a**–**e**, **4h**) (2 mmol) in CH_2Cl_2 (5 mL) was added *m*-CPBA (*m*-chloroperbenzoic acid) (75% purity, 6.8 mmol) at 0–5 °C. The mixture was stirred for 30 min, and the reaction completion was monitored through TLC. After completion of the reaction, reaction mixture was quenched with 20% aqueous $Na_2S_2O_3$ solution. The organic phase was separated and aqueous phase extracted thrice with ethyl acetate. The combined organic phase was washed with 1M NaOH solution and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated to afford the compounds (**5a**–**e**, **5h**) in excellent yields.

*6.12. 4-[2-(2-Fluoro-benzenesulfonyl)-ethyl]-2-(4-methoxy-phenyl)-5-methyl-2,4-dihydro-[1,2,4] triazol-3-one (**5a**)*

Purified by column chromatography (Petroleum ether/Ethyl acetate, 10/90); off white solid; yield: 98%, mp 191.2–193.4 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.77–7.73 (m, 1H, Ar–H), 7.67–7.61 (m, 1H, Ar–H), 7.56 (d, 2H, J = 8.96 Hz, Ar–H), 7.45–7.41 (m, 1H, Ar–H), 7.37–7.33 (m, 1H, Ar–H), 6.96 (d, 1H, J = 8.96 Hz, Ar–H), 4.01 (s, 4H, –CH_2–CH_2), 3.74 (s, 3H, O–CH_3), 2.27 (s, 3H, Ar–CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 159.2, 156.8, 151.2, 144.6, 137.5, 131.0, 129.8, 126.8, 125.7, 119.9, 117.7, 114.4, 55.7, 51.9, 36.3, 11.7. MS: m/z 392 [M + 1]; Anal. Calcd for $C_{18}H_{18}FN_3O_4S$: C, 55.23; H, 4.64; N, 10.74; S, 8.19. Found: C, 55.18; H, 4.65; N, 10.76; S, 8.21.

*6.13. 4-[2-(3-Fluoro-benzenesulfonyl)-ethyl]-2-(4-methoxy-phenyl)-5-methyl-2,4-dihydro-[1,2,4] triazol-3-one (**5b**)*

Purified by column chromatography (Petroleum ether/Ethyl acetate, 10/90); off white solid; yield: 97%; mp 193.2–195.5 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.79–7.76 (m, 2H, Ar–H), 7.69–7.65 (m, 1H, Ar–H), 7.63 (d, 2H, J = 9.08 Hz, Ar–H), 7.55–7.50 (m, 1H, Ar–H), 6.98 (d, 2H, J = 9.08 Hz, Ar–H), 3.99–3.96 (m, 4H, –CH_2), 3.75 (s, 3H, O–CH_3), 2.29 (s, 3H, Ar–CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.1, 156.8, 151.2, 144.2, 141.2, 132.2, 131.2, 124.1, 121.7, 119.8, 115.1, 114.5, 55.7, 51.4, 35.8, 11.75. MS: m/z 392 [M + 1]; Anal. Calcd for $C_{18}H_{18}FN_3O_4S$: C, 55.23; H, 4.64; N, 10.74; S, 8.19. Found: C, 55.31; H, 4.63; N, 10.74; S, 8.16.

*6.14. 4-[2-(4-Fluoro-benzenesulfonyl)-ethyl]-2-(4-methoxy-phenyl)-5-methyl-2,4-dihydro-[1,2,4] triazol-3-one (**5c**)*

Purified by column chromatography (Petroleum ether/Ethyl acetate, 10/90); off white solid; yield: 95%; mp 168.3–169.5 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.99–7.96 (m, 2H, Ar–H), 7.63 (d, 2H, J = 9.00 Hz, Ar–H), 7.43 (m, 2H, Ar–H), 6.98 (d, 2H, J = 9.00 Hz, Ar–H), 3.99–3.96 (m, 2H, –CH_2), 3.92–3.89 (m, 2H, –CH_2), 3.76 (s, 3H, O–CH_3), 2.29 (s, 3H, Ar–CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.5, 156.8, 151.2, 144.7, 135.6, 131.2, 119.9, 117.2, 116.9, 114.5, 55.7, 52.1, 35.9, 11.7. MS: m/z 392 [M + 1]; Anal. Calcd for $C_{18}H_{18}FN_3O_4S$: C, 55.23; H, 4.64; N, 10.74; S, 8.19. Found: C, 55.29; H, 4.64; N, 10.71; S, 8.20.

*6.15. 2-(4-Methoxy-phenyl)-5-methyl-4-[2-(3-trifluoromethylbenzenesulfonyl)-ethyl]-2,4-dihydro-[1,2,4] triazol-3-one (**5d**)*

Purified by column chromatography (Petroleum ether/Ethyl acetate, 10/90); off white solid; yield: 98%; mp 138.2–140.4 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.22–8.21 (m, 2H, Ar–H), 8.01 (d, 1H, J = 7.8 Hz, Ar–H), 7.81 (t, 1H, J = 8.00 Hz, Ar–H), 7.60 (d, 2H, J = 9.16 Hz, Ar–H), 6.95 (d, 2H, J = 9.16 Hz, Ar–H), 4.05–3.99 (m, 4H, –CH_2), 3.75 (s, 3H, O–CH_3), 2.28 (s, 3H, Ar–CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ 156.4, 150.8, 144.3, 140.1, 131.5, 131.2, 130.9, 130.7, 124.4, 124.2, 119.4, 114.1, 55.3, 51.5, 35.3, 11.3. MS: m/z 442 [M + 1]; Anal. Calcd for $C_{19}H_{18}F_3N_3O_4S$: C, 51.70; H, 4.11; N, 9.52; S, 7.26. Found: C, 51.79; H, 4.10; N, 9.42; S, 7.23.

*6.16. 4-[2-(4-Bromo-benzenesulfonyl)-ethyl]-2-(4-methoxy-phenyl)-5-methyl-2,4-dihydro-[1,2,4] triazol-3-one (**5e**)*

Purified by column chromatography (Petroleum ether/Ethyl acetate, 20/80); pale yellow solid; yield: 90%; mp 177.2–179.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68–7.62 (m, 6H, Ar–H), 6.93–6.91 (m, 2H, Ar–H), 4.12 (m, 2H, –CH_2), 3.82 (s, 3H, O–CH_3), 3.76 (m, 2H, –CH_2), 2.41 (s, 3H, Ar–CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ 156.8, 151.2, 144.7, 138.5, 132.9, 131.1, 129.8, 128.7, 119.9, 114.5, 55.7, 51.9, 35.9, 11.7. MS: m/z 452.0 [M +] and 454.0 [M + 2]; Anal. Calcd for $C_{18}H_{18}BrN_3O_4S$: C. 47.8; H. 4.01; N. 9.29; S. 7.09. Found: C, 47.88; H, 4.02; N, 9.30; S; 7.06.

6.17. 4-(2-Benzenesulfonyl-ethyl)-2-(4-methoxy-phenyl)-5-methyl-2,4-dihydro-[1,2,4] triazol-3-one (**5h**)

Purified by column chromatography (Petroleum ether/Ethyl acetate, 20/80); pale yellow solid; yield: 95%; mp 181.9–183.2 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.91 (d, 2H, J = 9.10 Hz, Ar–H), 7.68–7.59 (m, 5H, Ar–H), 6.98 (d, 2H, J = 9.10 Hz, Ar–H), 3.97 (t, 2H, J = 6.14 Hz, $-CH_2$), 3.86 (t, 2H, J = 6.14 Hz, $-CH_2$), 3.76 (s, 3H, O–CH_3), 2.27 (s, 3H, Ar–CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ 156.8, 151.5, 144.7, 139.3, 134.4, 131.2, 129.8, 127.8, 120.0, 114.5, 55.7, 52.11, 35.9, 11.7. MS: m/z 374.2 [M + 1]; Anal. Calcd for $C_{18}H_{19}N_3O_4S$: C. 57.90; H. 5.13; N.11.25; S. 8.59. Found: C, 57.78; H, 5.11; N, 11.23; S; 8.61.

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