Organic compounds incorporating ring systems continue to attract considerable interest due to their wide range of biological activities. In this context, heterocyclic compounds bearing 1,2,4-triazole scaffolds find wide application both in medicinal chemistry as well as agricultural science such as antibacterial [1], antimicrobial [2], antidepressant [3], anti-inflammatory [4], antiviral [5], anti-asthmatic [6], anticonvulsant [7], potent fungicides [8], herbicides [9] and insecticides [10]. A large number of sulfur-containing 1,2,4-triazoles are known for their biological activities [11-13]. Several compounds containing 1,2,4-triazole rings are well known as drugs. For example, fluconazole is used as an antimicrobial drug [14], while vorozole, letrozole and anastrozole are non-steroidal drugs used for the treatment of cancer [15] and loreclezole is used as an anticonvulsant [16].

Currently cancer is one of the causes of death and it is likely become the most common disease in the near future. The incidence and mortality of cancer patients have become one of the important issues discussed worldwide. Unfortunately, development of resistance to chemotherapeutic agents is a common obstacle in the treatment of different types of cancer [17, 18]. Several important drugs including 5-fluouracil (5FU), doxorubicin, celecoxib, mitoxantrone, hydrazine carbathioamide and indomethacin with different structures and mechanisms of antitumor activities fail to end these problems completely. Due to several side effects, drugs resistance and failure of antitumor drugs to exert their effects in certain cases of cancer, looking for new chemotherapeutic agents with synthesis or natural origin is one of the hot topics in cancer research laboratories.

Pokhodylo et al. [19] synthesized 1,2,3-triazoles derivatives with heterocyclic fragments according to the convenient synthetic procedures. The antitumor activity of the synthesized compounds was tested in NC160 cell lines. It was observed that some compounds showed moderate anticancer activity. Singha et al. [20] synthesized a
series of potential bioactive 4-amino-5-mercapto-3-aryl-1,2,4-triazoles according the 
literature methods. The synthesized compounds were characterized by spectroscopy 
and evaluated their anticancer activity against EAC (Ehrlich Ascites Carcinoma). 
Ying-Chao Duan et al. [21] synthesized a series of novel 1,2,3-
triazolethiosemicarbazide hybrids and their antiproliferative activity was evaluated 
against four human cancer lines. The results showed that number of hybrids exhibited 
potent activity in selected human cancer cell lines. In this chapter, a series of new S-
alkylated bis-1,2,4-triazole derivatives have been synthesized and their 
antiproliferative activity were determined. All the synthesized compounds 
characterized by elemental analyses, LC-MS and $^1$H NMR spectral studies.

8.2. Experimental

Materials and methods are described in Chapter-II, Section 2.2.1.

8.2.1. Synthesis of 2,2-malonylbis(N-(4-fluorophenyl)hydrazine-1-carbothiamide 
(29)

To an ethanolic solution of 28 (0.10 mmol), 4-fluorophenyl isothiocyanate 
(0.25 mmol) was added. The reaction mixture mass refluxed on steam bath for 4 h. 
Reaction mixture was then concentrated and then isolated with diethyl ether, as white 
solid. $^1$H NMR (DMSO-$d_6$, 300 MHz): $\delta = 3.91$ (s, 1H, CH$_2$), 7.20 (dd, $J = 4.95$, 8.40 
Hz, 2H, Ar-H), 7.55 (d, $J = 8.51$ Hz, 2H, Ar-H), 8.32 (s, 1H, NH), 10.17 (s, 1H, NH), 
11.30 (s, 1H, NH).

8.2.2. Synthesis of 5,5-methylenebis(4-(4-fluorophenyl)-4H-1,2,4-triazole-3-thiol) 
(30)

A suspension of 29 (0.10 mmol) in ethanol (25 ml) was dissolved in aq. 
NaOH (4N, 10 ml) and refluxed for 4h. The resulting solution was cooled, filtered and 
the product was recrystallized from methanol. $^1$H NMR (DMSO-$d_6$, 300 MHz): $\delta = 
3.91$ (s, 1H, CH$_2$), 7.21 (dd, $J = 4.95$, 8.90 Hz, 2H, Ar-H), 7.34 (d, $J = 8.64$ Hz, 2H, 
Ar-H), 13.84 (s, 1H, SH).
8.2.3. General procedure for the synthesis of bis(5-((benzyl)thio)-4-(4-fluorophenyl)-4H-1,2,4-triazol-3-yl)methane (31a-n)

To a stirred solution of 30 (0.01 mmol) and KOH (0.05 mmol) in ethanol (10 ml), substituted benzyl bromides (0.022 mmol) were added. The resulting mixture was stirred for 4 h at room temperature and the reaction was monitored by TLC. Reaction mass was concentrated and then water (10 ml) was added. Product was extracted with dichloromethane and the organic layer was washed with water, dried with Na₂SO₄ and concentrated. The purification of the residue by recrystallization from ethanol yielded the desired compounds 31(a-n). The title compounds were synthesized using the synthetic strategy described in Scheme 8.1.

![Scheme 8.1](image-url)
8.2.3.1. Bis(5-((benzyl)thio)-4-(4-fluorophenyl)-4H-1,2,4-triazol-3-yl)methane (31a)

This compound was prepared by the reaction of compound 30 and benzylbromide. It was obtained as a white solid. $^1$H NMR (DMSO-d$_6$, 400 MHz.): $\delta =$ 4.02 (s, 1H, CH$_2$), 4.3 (s, 2H, S-CH$_2$), 7.21 (dd, $J = 4.95$, 8.90 Hz, 2H, Ar-H), 7.27-7.33 (m, 5H, Ar-H), 7.39 (d, $J = 8.61$ Hz, 2H, Ar-H). MS (ESI) m/z: 583.1 (M+H$^+$). Anal. Calcd. for C$_{31}$H$_{24}$F$_2$N$_6$S$_2$ (%): C, 63.90; H, 4.15; N, 14.42. Found: C, 63.80; H, 4.12; N, 14.47.

8.2.3.2. Bis(5-((2-chlorobenzyl)thio)-4-(4-fluorophenyl)-4H-1,2,4-triazol-3-yl)methane (31b)

This compound was prepared by the reaction of compound 30 and 2-chlorobenzyl bromide. It was obtained as a white solid. $^1$H NMR (DMSO-d$_6$, 400 MHz.): $\delta =$ 3.99 (s, 1H, CH$_2$), 4.29 (s, 2H, S-CH$_2$), 7.20 (dd, $J = 4.94$, 8.93 Hz, 2H, Ar-H), 7.31-7.38 (m, 4H, Ar-H), 7.60-7.67 (m, 2H, Ar-H). MS (ESI) m/z: 650.2 (M$^+$), 652.2 (M+2). Anal. Calcd. for C$_{31}$H$_{22}$Cl$_2$F$_2$N$_6$S$_2$ (%): C, 57.14; H, 3.40; N, 12.90. Found: C, 57.18; H, 3.45; N, 12.88.

8.2.3.3. Bis(5-((3-chlorobenzyl)thio)-4-(4-fluorophenyl)-4H-1,2,4-triazol-3-yl)methane (31c)

This compound was prepared by the reaction of compound 30 and 3-chlorobenzyl bromide. It was obtained as a white solid. $^1$H NMR (DMSO-d$_6$, 400 MHz.): $\delta =$ 3.99 (s, 1H, CH$_2$), 4.31 (s, 2H, S-CH$_2$), 7.18 (dd, $J = 4.92$, 8.80 Hz, 2H, Ar-H), 7.33-7.41 (m, 4H, Ar-H), 7.64-7.67 (m, 2H, Ar-H), 7.57 (s, 1H, Ar-H). MS (ESI) m/z: 650.2 (M$^+$), 652.2 (M+2). Anal. Calcd. for C$_{31}$H$_{22}$Cl$_2$F$_2$N$_6$S$_2$ (%): C, 57.14; H, 3.40; N, 12.90. Found: C, 57.10; H, 3.39; N, 12.94.

8.2.3.4. Bis(5-((4-chlorobenzyl)thio)-4-(4-fluorophenyl)-4H-1,2,4-triazol-3-yl)methane (31d)

This compound was prepared by the reaction of compound 30 and 4-chlorobenzyl bromide. It was obtained as a white solid. $^1$H NMR (DMSO-d$_6$, 400 MHz.): $\delta =$ 4.0 (s, 1H, CH$_2$), 4.3 (s, 2H, S-CH$_2$), 7.21 (dd, $J = 4.95$, 8.90 Hz, 2H, Ar-H), 7.34-7.43 (m, 4H, Ar-H), 7.53 (d, $J = 8.88$ Hz, 2H, Ar-H). MS (ESI) m/z: 650.2 (M$^+$), 652.2 (M+2). Anal. Calcd. for C$_{31}$H$_{22}$Cl$_2$F$_2$N$_6$S$_2$ (%): C, 57.14; H, 3.40; N, 12.90. Found: C, 57.11; H, 3.42; N, 12.88.
8.2.3.5. **Bis(5-((4-fluorobenzyl)thio)-4-(4-fluorophenyl)-4H-1,2,4-triazol-3-yl) methane (31e)**

This compound was prepared by the reaction of compound 30 and 4-fluorobenzyl bromide. It was obtained as a white solid. \(^1\)H NMR (DMSO-\(d_6\), 400 MHz): \(\delta = 4.02\) (s, 1H, CH\(_2\)), \(4.29\) (s, 2H, S-CH\(_2\)), \(7.25\) (m, \(J = 8.46\) Hz, 4H, Ar-H), \(7.39\) (d, \(J = 8.67\) Hz, 2H, Ar-H), \(7.55\) (d, \(J = 8.12\) Hz, 2H, Ar-H). MS (ESI) m/z: 619.6 (M+H). Anal. Calcd. for C\(_{31}\)H\(_{22}\)F\(_4\)N\(_6\)S\(_2\): C, 60.18; H, 3.58; N, 13.58. Found: C, 60.22; H, 3.54; N, 13.60.

8.2.3.6. **Bis(5-((2-fluorobenzyl)thio)-4-(4-fluorophenyl)-4H-1,2,4-triazol-3-yl) methane (31f)**

This compound was prepared by the reaction of compound 30 and 2-fluoroobenzyl bromide. It was obtained as a white solid. \(^1\)H NMR (DMSO-\(d_6\), 400 MHz): \(\delta = 4.0\) (s, 1H, CH\(_2\)), \(4.3\) (s, 2H, S-CH\(_2\)), \(7.15-7.25\) (m, 3H, Ar-H), \(7.33-7.40\) (m, 3H, Ar-H), \(7.64-7.67\) (m, 1H, Ar-H). MS (ESI) m/z: 619.6 (M+H). Anal. Calcd. for C\(_{31}\)H\(_{22}\)F\(_4\)N\(_6\)S\(_2\): C, 60.18; H, 3.58; N, 13.58. Found: C, 60.20; H, 3.53; N, 13.64.

8.2.3.7. **Bis(4-(4-fluorophenyl)-5-(4-methylbenzyl)thio)-4H-1,2,4-triazol-3-yl) methane (31g)**

This compound was prepared by the reaction of compound 30 and 4-methylbenzyl bromide. It was obtained as a white solid. \(^1\)H NMR (DMSO-\(d_6\), 400 MHz): \(\delta = 2.28\) (s, 3H, CH\(_3\)), \(4.01\) (s, 1H, CH\(_2\)), \(4.29\) (s, 2H, S-CH\(_2\)), \(7.14\) (d, \(J = 8.0\) Hz, 2H, Ar-H), \(7.21\) (dd, \(J = 4.95, 8.90\) Hz, 2H, Ar-H), \(7.32-7.40\) (m, 4H, Ar-H). MS (ESI) m/z: 611.4 (M+H). Anal. Calcd. for C\(_{31}\)H\(_{22}\)F\(_4\)N\(_6\)S\(_2\): C, 64.90; H, 4.62; N, 13.76. Found: C, 64.87; H, 4.60; N, 13.64.

8.2.3.8. **Bis(4-(4-fluorophenyl)-5-(4-methoxybenzyl)thio)-4H-1,2,4-triazol-3-yl) methane (31h)**

This compound was prepared by the reaction of compound 30 and 4-methoxybenzyl bromide. It was obtained as a white solid. \(^1\)H NMR (DMSO-\(d_6\), 400 MHz): \(\delta = 3.68\) (s, 3H, O-CH\(_3\)), \(3.99\) (s, 1H, CH\(_2\)), \(4.29\) (s, 2H, S-CH\(_2\)), \(6.88\) (d, \(J = 8.5\) Hz, 2H, Ar-H), \(7.20\) (dd, \(J = 4.93, 8.91\) Hz, 2H, Ar-H), \(7.35-7.44\) (m, 4H, Ar-H).
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MS (ESI) m/z: 642.6 (M+H)+. Anal. Calcd. for C_{33}H_{28}F_{2}N_{6}O_{2}S_{2} (%): C, 61.67; H, 4.39; N, 13.08. Found: C, C, 61.60; H, 4.45; N, 13.12.

8.2.3.9. Bis(4-(4-fluorophenyl)-5-(3-methoxybenzyl)thio)-4H-1,2,4-triazol-3-yl) methane (31i)

This compound was prepared by the reaction of compound 30 and 3-methoxybenzyl bromide. It was obtained as a white solid; H NMR (DMSO-d_6, 400 MHz,): δ = 3.68 (s, 3H, O-CH_3), 3.98 (s, 1H, CH_2), 4.28 (s, 2H, S-CH_2), 6.79-6.83 (m, 3H, Ar-H), 7.11-7.20 (m, 3H, Ar-H), 7.34 (d, J = 8.82 Hz, 2H, Ar-H). MS (ESI) m/z: 642.6 (M+H)+. Anal. Calcd. for C_{33}H_{28}F_{2}N_{6}O_{2}S_{2} (%): C, 61.67; H, 4.39; N, 13.12. Found: C, 63.55; H, 4.19; N, 13.17.

8.2.3.10. Bis(4-(4-fluorophenyl)-5-(3-(trifluoromethyl)benzyl)thio)-4H-1,2,4-triazol-3-yl) methane (31j)

This compound was prepared by the reaction of compound 30 and 3-(trifluoromethyl)benzyl bromide. It was obtained as a yellow solid; H NMR (DMSO-d_6, 400 MHz,): δ = 4.02 (s, 1H, CH_2), 4.3 (s, 2H, S-CH_2), 7.21 (dd, J = 4.95, 8.90 Hz, 2H, Ar-H), 7.38 (d, J = 8.61 Hz, 2H, Ar-H), 7.76 (d, J = 8.8 Hz, 2H, Ar-H), 8.21 (d, J = 8.9 Hz, 2H, Ar-H). MS (ESI) m/z: 673.5 (M+H)+. Anal. Calcd. for C_{31}H_{23}F_{2}N_{6}O_{4}S_{2} (%): C, 55.35; H, 3.30; N, 16.66. Found: C, 55.32; H, 3.34; N, 16.61.

8.2.3.11. Bis(4-(4-fluorophenyl)-5-(4-nitrobenzyl)thio)-4H-1,2,4-triazol-3-yl) methane (31k)

This compound was prepared by the reaction of compound 30 and 4-nitrobenzyl bromide. It was obtained as a yellow solid; H NMR (DMSO-d_6, 400 MHz,): δ = 4.02 (s, 1H, CH_2), 4.3 (s, 2H, S-CH_2), 7.21 (dd, J = 4.95, 8.90 Hz, 2H, Ar-H), 7.38 (d, J = 8.61 Hz, 2H, Ar-H), 7.76 (d, J = 8.8 Hz, 2H, Ar-H), 8.21 (d, J = 8.9 Hz, 2H, Ar-H). MS (ESI) m/z: 673.5 (M+H)+. Anal. Calcd. for C_{31}H_{23}F_{2}N_{6}O_{4}S_{2} (%): C, 55.35; H, 3.30; N, 16.66. Found: C, 55.32; H, 3.34; N, 16.61.
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MHz): δ = 3.99 (s, 1H, CH₂), 4.29 (s, 2H, S-CH₂), 7.11 (d, J = 8.88 Hz, 2H, Ar-H), 7.20 (dd, J = 8.90 Hz, 2H, Ar-H), 7.29 (d, J = 8.84 Hz, 2H, Ar-H), 7.82 (d, J = 8.44 Hz, 2H, Ar-H). MS (ESI) m/z: 737.9 (M⁺), 739.9 (M+2).


8.2.3.13. Bis(5-((5-chloro-2-fluorobenzyl)thio)-4-(4-fluorophenyl)-4H-1,2,4-triazol-3-yl)methane (31m)

This compound was prepared by the reaction of compound 30 and 5-chloro-2-fluorobenzyl bromide. It was obtained as a white solid. ¹H NMR (DMSO-d₆, 400 MHz): δ = 3.99 (s, 1H, CH₂), 4.28 (s, 2H, S-CH₂), 7.16-7.23 (m, 3H, Ar-H), 7.28-7.40 (m, 3H, Ar-H), 7.43-7.47 (m, 1H, Ar-H). MS (ESI) m/z: 688.4 (M⁺), 690.4 (M+2). Anal. Calcd. for C₃₁H₂₀Cl₂F₄N₆S₂ (%): C, 54.15; H, 2.93; N, 12.22. Found: C, 54.20; H, 3.33; N, 16.50.

8.2.3.14. Bis(4-(4-fluorophenyl)-5-(4-(trifluoromethyl)benzyl)thio)-4H-1,2,4-triazol-3-yl)methane (31n)

This compound was prepared by the reaction of compound 30 and 4-(trifluoromethyl)benzyl bromide. It was obtained as a white solid. ¹H NMR (DMSO-d₆, 400 MHz): δ = 4.03 (s, 1H, CH₂), 4.29 (s, 2H, S-CH₂), 7.14-7.21 (m, 4H, Ar-H), 7.32 (d, J = 8.80 Hz, 2H, Ar-H), 7.40 (d, J = 8.86 Hz, 2H, Ar-H), 7.54 (d, J = 8.90 Hz, 2H, Ar-H). MS (ESI) m/z: 719.7 (M+H)⁺. Anal. Calcd. for C₃₃H₂₂F₈N₆S₂ (%): C, 55.15; H, 3.09; N, 11.69. Found: C, 55.12; H, 3.07; N, 11.72.

8.2.4. Antiproliferative activity

Experimental procedure is explained in Chapter-II, Section 2.2.3.

8.3. Results and discussion

8.3.1. Spectral studies

The chemical structures of the new compounds are given in Table 8.1. In the present work, a series of ten new compounds were synthesized and the structure of the compounds was established on the basis of ¹H NMR and mass spectral data. The proton spectral data of 30 shows resonance at δ 13.84 ppm (s, SH) and at δ 7.2-
7.55 ppm (4H, Ar-H). But the product contains two SH groups and 8 aromatic protons, this is because compound 30 contains equivalent groups at both the sides. The $^1$H NMR spectra of 31i and 31m are shown in Figures 8.1 and 8.2. Similarly in all the synthesized compounds 31(a-n), we observed half-proton spectra, because of equivalent sides. The LC-MS of 31i and 31m (Figures 8.3 and 8.4) showed molecular ion peaks which are in agreement with their molecular formula. The elemental analyses data showed good agreement between the experimentally determined values and the theoretically calculated values within ± 0.4 %.

Table 8.1. Chemical structure and physical data of new bistriazoles 31(a-n)

<table>
<thead>
<tr>
<th>Compound</th>
<th>R</th>
<th>Structure</th>
<th>Yield (%)</th>
<th>m.p. (°C)</th>
</tr>
</thead>
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<td></td>
<td><img src="image1" alt="structure" /></td>
<td>86</td>
<td>204-206</td>
</tr>
<tr>
<td>31b</td>
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<tr>
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<td>85</td>
<td>158-160</td>
</tr>
<tr>
<td>31f</td>
<td></td>
<td><img src="image6" alt="structure" /></td>
<td>84</td>
<td>164-166</td>
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</table>
31g

31h

31i

31j

31k

31l

31m

31n

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Figure 8.1: $^1$H NMR spectrum of bis(4-(4-fluoropheny)-5-(3-methoxybenzyl)thio)-4H-1,2,4-triazol-3-yl) methane (31i).
Figure 8.2: $^1$H NMR spectrum of bis(5-((5-chloro-2-fluorobenzyl)thio)-4-(4-fluorophenyl)-4H-1,2,4-triazol-3-yl)methane (31m).
Figure 8.3: LC-MS of bis(4-(4-fluorophenyl)-5-(3-methoxybenzyl)thio)-4H-1,2,4-triazol-3-yl) methane (31i).
Figure 8.4: LC-MS of bis(5-((5-chloro-2-fluorobenzyl)thio)-4-(4-fluorophenyl)-4H-1,2,4-triazol-3-yl)methane (31m).
8.3.2. Antiproliferative activity

The antiproliferative action of compounds 31(a–n) was tested against four different cell lines. Fluorine containing compounds are well known to play an important role in biochemistry [22, 23]. The activity was evaluated by measuring the levels of surviving cells after incubation for 24 h with the test samples, using the MTT colorimetric assay, based on the ability of metabolically active cells to convert the pale yellow MTT to a blue formazan product which is quantifiable spectrophotometrically. Percentage of cell survival for tested compounds against four cell lines was tabulated in Table 8.2.

The results of the biological screening experiments revealed that within the library of compounds 31(a–n), three compounds 31j and 31n showed good activity and the remaining compounds showed moderate activity. These compounds contain trifluoromethyl substituent on the benzene ring at different position. Among the compounds, compound 31j exhibited 74 %, 78 % and 71 % (at 10µM) inhibitory activity against Colo-205, MDA-MB 231 and IMR-32 cell lines, respectively, whereas compound 31n showed less inhibitory activity against K562. The good inhibition by these compounds could be attributed to the presence of electron withdrawing trifluoromethyl group. Similarly, compound 31m showed 70 %, 69 % and 66 % antiproliferation against Colo-205, MDA-MB 231 and IMR-32 cell lines, respectively. Compounds 31e and 31f are more potent than difluorinated 1,2,4-triazole compounds. Similarly, other compounds in the series showed moderate activity. However, the presence of electron withdrawing groups in the phenyl ring increased the antiproliferative efficacy. Based on their growth inhibitory activity data on cancer cells, monofluorine and trifluoromethyl-containing 1,2,4-triazole compounds were found to effectively inhibit the growth of cancer cells. The role of 1,2,4-triazole and electron withdrawing groups on the benzene ring are important for antiproliferative activity, and it is common in all derivatives.
Table 8.2. Antiproliferative activity of 31(a-n) against human cancer cells determined by MTT test

<table>
<thead>
<tr>
<th>Compound</th>
<th>% Cell survival at 10µM</th>
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</thead>
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<tr>
<td></td>
<td>K562</td>
</tr>
<tr>
<td>31a</td>
<td>- *</td>
</tr>
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<td>- *</td>
</tr>
<tr>
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<td>- *</td>
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</tr>
<tr>
<td>31m</td>
<td>65.21</td>
</tr>
<tr>
<td>31n</td>
<td>69.34</td>
</tr>
<tr>
<td>Control</td>
<td>100</td>
</tr>
</tbody>
</table>

*Represents ≤ 30 % Cell survival

8.4. Conclusion

In conclusion, a series of new bis-1,2,4-triazole derivatives 31(a-n) were synthesized and their antiproliferative activity has been evaluated. Antiproliferative assay results indicated that these derivatives have high antiproliferative activity against Colo-205, IMR-32 and MDA-MB 231. Compounds 31j and 31n containing trifluoromethyl group appeared to be the most active against the cell lines. From the experimental results, it could be concluded that the introduction of the 1,2,4-triazole moiety and electron withdrawing groups has significant potential to obtain new antiproliferative compounds.
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