SYNTHESIS, CHARACTERIZATION AND ANTIFUNGAL ACTIVITY OF SOME NOVEL GRAMINE BEARING 1,2,4-TRIAZOLES

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ABSTRACT

A series of novel 5-(3-dimethylaminomethyl-indol-1-ylmethyl)-4-phenyl-4H-[1,2,4]triazole-3-thiols (5a-f) were synthesized from N-phenyl-[(3-dimethylaminomethyl-indol-1-yl)acetyl]-hydrazinecarbothioamides (4a-f) through cyclization reaction. The synthesis of the title compounds commenced form commercially available (1H-indol-3-ylmethyl)-dimethyl-amine (gramine) (1) and by involving (3-dimethylaminomethyl-indol-1-yl)-acetic acid ethyl ester (2) and (3-dimethylaminomethyl-indol-1-yl)-acetic acid hydrazide (3) as intermediates. The chemical structures of the all newly synthesized compounds were elucidated by their IR, ¹H and ¹³C NMR, mass spectral data and elemental analysis. Further, the target compounds were used to find their antifungal activity against various microorganisms.

Keywords: Gramine, 1,2,4-Triazoles, Antifungal activity.

INTRODUCTION

In the last few decades, the chemistry of 1,2,4-triazole and their derivatives has received considerable attention owing to their synthetic and effective biological importance. For example, a large number of 1,2,4-triazole-containing ring system have been incorporated into a wide variety of biological activities such as antibacterial [1], antifungal [2], antitubercular [3], antimycobacterial [4], anticancer [5], antiviral [6].

RESULTS AND DISCUSSION

Based on these observations, inspired by the biological profile of 1,3,4-triazoles and their increasing importance in pharmaceutical and biological fields and in continuation of our research on biologically active heterocycles, we have introduced 1,3,4-triazole moiety on gramine ring which leads to the presence of both active pharmacophores in a single molecular framework for the intensified biological activities. Thus we have designed and synthesized a series of novel 5-(3-dimethylaminomethyl-indol-1-ylmethyl)-4-phenyl-4H-[1,2,4]triazole-3-thiols (5a-f) in good to excellent yields by involving (3-dimethylaminomethyl-indol-1-yl)-acetic acid ethyl ester (2), (3-dimethylaminomethyl-indol-1-yl)-acetic acid hydrazide (3) and N-phenyl-[(3-dimethylaminomethyl-indol-1-yl)acetyl]-hydrazinecarbothioamides (4a-f) as intermediates and commercially available (1H-indol-3-ylmethyl)-dimethyl-amine (1) as raw material. The synthetic route leading to the title compounds is summarized in scheme 1. Thus the initial intermediate 2 has been prepared on esterification with chloro ethylacetate and K$_2$CO$_3$ in acetone solvent at room temperature on uniform stirring for 12 h. Further, the intermediate 2 on condensation with hydrazine hydrate in methanol at room temperature on constant stirring for 6 h to give the next intermediate 3. The final intermediates 4a-f have been synthesized from intermediate 3 on treatment with different aryl isothiocyanates in ethanol solvent on uniform stirring at room temperature for 3-4 h. Finally, the intermediates 4a-f on cyclization in presence of NaOH solution at ambient temperature on uniform stirring for 5-6 h afforded the corresponding target compounds 5a-f in good to excellent yields. The chemical structures of the all newly synthesized compounds were elucidated by their IR, $^1$H and $^{13}$C NMR, mass spectral data and elemental analysis. Further, the target compounds were used to find their antifungal activity against various microorganisms.

Scheme 1: (i) ClCH$_2$CO$_2$C$_2$H$_5$, acetone, K$_2$CO$_3$, RT, 12h; (ii) NH$_2$NH$_2$.H$_2$O, methanol, RT, 6 h; (iii) Aryl/ substituted aryl isothiocyanate, ethanol, RT, 3-4 h; (iv) 2NaOH, RT, 5-6 h. 4/5(a) H; 5(b) 2-CH$_3$; 5(c) 2-OH; 5(d) 4-OCH$_3$; 5(e) 4-Cl; 5(f) 4-NH$_2$.
Table 1: The *in vitro* antifungal activity of compounds 5a-f [Minimum Inhibitory Con. (MIC, µg/mL)].

<table>
<thead>
<tr>
<th>Compound</th>
<th>C. albicans</th>
<th>A. Fumigatus</th>
<th>T. Rubrum</th>
<th>T. Mentropyhte</th>
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<tr>
<td>5a</td>
<td>25.0</td>
<td>12.5</td>
<td>&gt;50.0</td>
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<td>5b</td>
<td>25.0</td>
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<tr>
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<tr>
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<td>25.0</td>
<td>12.5</td>
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</tr>
<tr>
<td>Amphotericin B</td>
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<td>3.12</td>
<td>3.12</td>
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</tr>
</tbody>
</table>

**ANTIFUNGAL ACTIVITY**

The newly synthesized compounds 5a-f were screened for their antifungal activity against four fungal organisms viz., *Candida albicans*, *Aspergillus fumigatus*, *Trichophyton rubrum*, and *Trichophyton mentagrophytes* in dimethyl sulfoxide by broth dilution method [8]. For the antifungal assay, *C. albicans* was grown for 48 h at 28°C in YPD broth (1% yeast extract, 2% peptone, and 2% dextrose), harvested by centrifugation and then washed twice with sterile distilled water. *A. fumigatus*, *T. rubrum* and *T. mentagrophytes* were plated in potato dextrose agar and incubated at 28°C for two weeks. Spores were washed three times with sterile distilled water and resuspended in distilled water to obtain an initial inoculum size of $10^5$ spores/mL. Each test compound was dissolved in DMSO and diluted with potato dextrose broth (Difco) to prepare serial two-fold dilutions in the range of 100 to 0.8 µg/mL. Ten microliters of the broth containing about $10^3$ (for yeast) and $10^4$ (for filamentous fungi) cells/mL of test fungi was added to each well of a 96-well microtiter plate. Culture plates were incubated for ~48 to 72 h at 28 °C. The minimum inhibitory concentration (MIC, µg/mL) were measured and compared with the standard drug Amphotericin B, the MIC values of the compounds screened are given in Table 1. The antifungal screening data showed good activity of the test compounds. Among the screened compounds, 5c is highly active against *T. rubrum*, *T. mentagrophytes*, 5e is also active against only *C. albicans*. The activity of these compounds is bear to the standard. All the remaining tested compounds in this series exhibited either good or moderate activity towards different organisms. None of the compounds is inactive against any one of the organism.
EXPERIMENTAL SECTION

All reagents and solvents were used as purchased without further purification. Melting points were determined on a Fisher–Johns melting point apparatus and are uncorrected. Crude products were purified by column chromatography on silica gel of 60–120 mesh. IR spectra were recorded on a Perkin-Elmer BX series FTIR 5000 spectrometer using KBr pellet. NMR spectra were recorded on a Varian 300 MHz spectrometer for $^1$H NMR and 100 MHz spectrometer $^{13}$C NMR. The chemical shifts were reported as ppm down field using TMS as an internal standard. Mass spectra were recorded on a VG-Micromass 7070H spectrometer operating at 70 eV.

Synthesis of (3-dimethylaminoethyl-indol-1-yl)-acetic acid ethyl ester (2)

To a well stirred solution of (1H-indol-3-ylmethyl)-dimethyl-amine (1) (1 mmol) and potassium carbonate in acetone (20 ml) was added chloro ethylacetate (1 mmol) over a period of 10 min. The reaction mixture was constantly stirred at room temperature for 12 h. After completion of the reaction, (monitored by TLC), the mixture on cooling afforded the solid, which was recrystallized from petroleum ether to give pure (3-dimethylaminomethyl-indol-1-yl)-acetic acid ethyl ester (2).

Synthesis of (3-dimethylaminomethyl-indol-1-yl)-acetic acid hydrazide (3)

To a stirred solution of (3-dimethylaminomethyl-indol-1-yl)-acetic acid ethyl ester (2) (1 mmol) in methanol (10 ml) was drop wise added hydrazine hydrate (2 mmol). The mixture was stirred uniformly at ambient temperature for 6 h. After completion of the reaction (monitored by TLC), the separated product was filtered, washed with water, dried, and recrystallized from ethanol to form pure (3-dimethylaminomethyl-indol-1-yl)-acetic acid hydrazide (3).

Synthesis of N-phenyl-[(3-dimethylaminomethyl-indol-1-yl) acetyl]-hydrazinecarbothioamides (4a-f)

A mixture of (3-dimethylaminomethyl-indol-1-yl)-acetic acid hydrazide (3) and aryl isothiocyanate (1 mmol) in ethanol (10 ml) was stirred constantly at room temperature for 3-4 h. After completion of the reaction, (monitored by TLC), the solvent on evaporation resulted the crude product which was filtered and purified by recrystallization from ethanol to give the corresponding N-phenyl-[(3-dimethylaminomethyl-indol-1-yl)acetyl]-hydrazinecarbothioamides (4a-f) in pure form.
Synthesis of 5-(3-dimethylaminomethyl-indol-1-ylmethyl)-4-phenyl-4H-[1,2,4]triazole-3-thiols (5a-f)

A mixture of N-phenyl-[(3-dimethylaminomethyl-indol-1-yl) acetyl]-hydrazinecarbothioamides (4a-f) (1 mmol) and 10% sodium hydroxide (0.02 mmol) was stirred at room temperature for 5-6 h. After completion of the reaction, (monitored by TLC), the residual mass was poured over crushed ice and neutralized the alkaline solution with 10% hydrochloric acid. The precipitated crude product was filtered, washed with water, dried and recrystallized from ethanol to get the pure 5-(3-dimethylaminomethyl-indol-1-ylmethyl)-4-phenyl-4H-[1,2,4]triazole-3-thiols (5a-f).

PHYSICAL AND SPECTRAL DATA

(3-Dimethylaminomethyl-indol-1-yl)-acetic acid ethyl ester (2)

Orange solid, yield: 74%, mp: 125-127 °C; IR (KBr): 3028 (C=O), 1582 (C=O) cm\(^{-1}\); \(^1\)H NMR (300 MHz, DMSO-\(d_6\)): \(\delta\) 7.65-7.15 (m, 4H, Ar-H), 7.21 (s, 1H, CH), 4.02 (q, 2H, OCH\(_3\)), 3.21 (s, 2H, COCH\(_3\)), 2.32 (s, 2H, NCH\(_2\)), 1.27 (t, 3H, CH\(_3\)), 1.12 (s, 6H, 2XCH\(_3\)); \(^{13}\)C NMR (100 MHz, DMSO-\(d_6\)): \(\delta\) 172.8, 142.6, 133.8, 124.5, 122.3, 121.4, 115.6, 112.4, 110.3, 61.8, 59.7, 56.8, 43.6, 14.3.; MS: 260 m/z (M\(^+\)); Elemental analysis: Calculated for C\(_{15}\)H\(_{20}\)N\(_2\)O: C=69.20, H=7.74, N=10.76, O=12.29. Found: C=68.64, H=7.15, N=9.84, O=11.95.

(3-Dimethylaminomethyl-indol-1-yl)-acetic acid hydrazide (3)

Yellow solid, yield: 71%, mp: 136-138 °C; IR (KBr): 3342 (N=O), 3024 (C=H, Ar), 2965 (C-H, CH\(_3\)), 1665 (C=O), 1618 (C=C, Ar) cm\(^{-1}\); \(^1\)H NMR (300 MHz, DMSO-\(d_6\)): \(\delta\) 7.72-7.26 (m, 4H, Ar-H), 7.32 (s, 1H, CH), 3.26 (s, 2H, COCH\(_3\)), 2.37 (s, 2H, NCH\(_2\)), 1.18 (s, 6H, 2XCH\(_3\)), 7.65 (s, 1H, CONH), 5.54 (s, 2H, NH\(_2\)); \(^{13}\)C NMR (100 MHz, DMSO-\(d_6\)): \(\delta\) 173.2, 141.7, 133.8, 124.1, 121.0, 120.9, 115.7, 112.6, 111.4, 63.5, 57.4, 46.7; MS: 246 m/z (M\(^+\)); Elemental analysis: Calculated for C\(_{13}\)H\(_{18}\)N\(_4\)O: C=63.39, H=7.37, N=22.75, O=6.50. Found: C=62.34, H=7.02, N=21.84, O=6.14.

\(\text{N-Phenyl-[(3-dimethylaminomethyl-indol-1-yl)acetyl]-hydrazinecarbothioamide (4a)}\)

Gray solid, yield: 77%, mp: 130-132 °C; IR (KBr): 3163 (N-H), 3029 (C-H, Ar), 2972 (C-H, CH\(_3\)), 1672 (C=O), 1581 (C=C, Ar), 1372 (C=S) cm\(^{-1}\); \(^1\)H NMR (300 MHz, DMSO-\(d_6\)): \(\delta\) 7.76-7.19 (m, 9H, Ar-H), 7.72 (s, 1H, CONH), 7.64 (s, 1H, NHCS), 7.58 (s, 1H, NH-Ar), 7.19 (s, 1H, CH), 3.26 (s, 2H, COCH\(_3\)), 2.28 (s, 2H, NCH\(_2\)), 1.21 (s, 6H, 2XCH\(_3\)); \(^{13}\)C NMR (100 MHz, DMSO-\(d_6\)): \(\delta\) 173.6, 168.6, 141.2, 139.6, 133.6, 128.3, 126.5, 125.6, 124.7, 123.4,
121.8, 119.7, 116.2, 113.2, 64.8, 56.3, 43.8; MS: 381 m/z (M⁺); Elemental analysis: Calculated for C$_{20}$H$_{23}$N$_5$OS: C-62.97, H-6.08, N-18.36, O-4.19, S-8.41. Found: C-61.38, H-5.89, N-17.84, O-4.02, S-7.89.

**N-o-Tolyl-[(3-dimethylaminomethyl-indol-1-yl)acetyl]-hydrazinecarbothioamide (4b)**

Yellow solid, yield: 77%, mp: 121-123 °C; IR (KBr): 3236 (N-H), 3035 (C-H, Ar), 2958 (C-H, CH$_3$), 1668 (C=O), 1588 (C=C, Ar), 1365 (C=S) cm$^{-1}$; $^1$H NMR (300 MHz, DMSO-d$_6$): $\delta$ 10.88 (s, 1H, NH), 9.69 (s, 1H, CSNH), 9.31 (s, 1H, CONH), 7.70-7.26 (m, 8H, Ar-H), 7.28 (s, 1H, CH), 3.14 (s, 2H, COCH$_2$), 2.29 (s, 2H, NCH$_2$), 2.12 (s, 3H, CH$_3$), 1.25 (s, 6H, 2XCH$_3$); $^{13}$C NMR (100 MHz, DMSO-d$_6$): $\delta$ 177.6, 171.3, 146.3, 142.5, 136.7, 132.2, 128.4, 127.6, 126.3, 125.7, 124.5, 123.7, 120.7, 117.2, 115.2, 112.0, 64.3, 57.2, 43.8, 15.3; MS: 395 m/z (M⁺); Elemental analysis: Calculated for C$_{21}$H$_{25}$N$_5$OS: C-63.77, H-6.37, N-17.71, O-4.05, S-8.11. Found: C-62.01, H-6.06, N-16.98, O-3.95, S-7.84.

**N-2-Hydroxyphenyl-[(3-dimethylaminomethyl-indol-1-yl)acetyl]-hydrazinecarbothioamide (4c)**

Brown solid, yield: 73%, mp: 155-157 °C; IR (KBr): 3345 (O-H), 3268 (N-H), 3025 (C-H, Ar), 2974 (C-H, CH$_3$), 1672 (C=O), 1574 (C=C, Ar), 1364 (C=S) cm$^{-1}$; $^1$H NMR (300 MHz, DMSO-d$_6$): $\delta$ 11.21 (s, 1H, O-H), 10.95 (s, 1H, NH), 9.80 (s, 1H, CSNH), 9.35 (s, 1H, CONH), 7.70-7.20 (m, 8H, Ar-H), 7.21 (s, 1H, CH), 3.19 (s, 2H, COCH$_2$), 2.37 (s, 2H, NCH$_2$), 1.21 (s, 6H, 2XCH$_3$); $^{13}$C NMR (100 MHz, DMSO-d$_6$): $\delta$ 175.2, 171.1, 153.2, 141.2, 133.5, 128.2, 126.3, 125.4, 124.8, 123.0, 122.7, 121.0, 119.8, 117.8, 115.2, 112.0, 66.5, 58.4, 44.2; MS: 397 m/z (M⁺); Elemental analysis: Calculated for C$_{20}$H$_{25}$N$_5$O$_2$S: C-60.43, H-5.83, N-17.62, O-8.05, S-8.07. Found: C-59.54, H-5.21, N-16.89, O-7.84, S-7.94.

**N-4-Methoxyphenyl-[(3-dimethylaminomethyl-indol-1-yl)acetyl]-hydrazinecarbothioamide (4d)**

Yellow solid, yield: 77%, mp: 141-142 °C; IR (KBr): 3152 (N-H), 3027 (C-H, Ar), 2979 (C-H, CH$_3$), 1672 (C=O), 1582 (C=C, Ar), 1378 (C=S) cm$^{-1}$; $^1$H NMR (300 MHz, DMSO-d$_6$): $\delta$ 10.92 (s, 1H, NH), 9.78 (s, 1H, CSNH), 9.32 (s, 1H, CONH), 7.74-7.26 (m, 4H, Ar-H), 7.58 (d, 2H, J = 7.2 Hz, CH), 7.42 (d, 2H, J = 7.2 Hz, CH), 7.27 (s, 1H, CH), 3.31 (s, 2H, COCH$_2$), 2.41 (s, 2H, NCH$_2$), 2.32 (s, 3H, CH$_3$), 1.28 (s, 6H, 2XCH$_3$); $^{13}$C NMR (100 MHz, DMSO-d$_6$): $\delta$ 176.3, 162.3, 154.8, 142.3, 135.7, 131.0, 128.6, 126.3, 124.5, 122.1, 118.9, 116.2, 114.3, 112.7, 64.2, 57.6, 55.6, 46.5; MS: 411 m/z (M⁺); Elemental analysis: Calculated for
C_{21}H_{25}N_{5}O_{2}S: C=61.29, H=6.12, N=17.02, O=7.78, S=7.79. Found: C=60.54, H=5.84, N=16.74, O=7.02, S=7.07.

**N-4-Chlorophenyl-[(3-dimethylaminomethyl-indol-1-yl)acetyl]-hydrazinecarbothioamide (4e)**

Pale yellow solid, yield: 71%, mp: 131-133 °C; IR (KBr): 3218 (N-H), 3016 (C-H, Ar), 2970 (C-H, CH_{3}), 1672 (C=O), 1565 (C=C, Ar), 1382 (C=S) cm^{-1}; \(^1\)H NMR (300 MHz, DMSO-d_{6}): δ 10.84 (s, 1H, NH), 9.34 (s, 1H, CSNH), 9.26 (s, 1H, CONH), 7.76-7.18 (m, 4H, Ar-H), 7.52 (d, 2H, J = 7.0 Hz, Ar), 7.49 (d, 2H, J = 7.0 Hz, CH), 7.30 (s, 1H, CH), 3.28 (s, 2H, COCH_{2}), 2.37 (s, 2H, NCH_{2}), 1.23 (s, 6H, 2XCH_{3}); \(^{13}\)C NMR (100 MHz, DMSO-d_{6}): δ 178.2, 172.3, 146.5, 137.2, 130.2, 126.3, 125.7, 124.2, 123.7, 122.7, 121.4, 116.7, 114.2, 112.8, 65.3, 59.6, 43.2; MS: 415 m/z (M^+); Elemental analysis: Calculated for C_{20}H_{22}ClN_{3}OS: C=57.75, H=5.33, Cl=8.52, N=16.84, O=3.85, S=7.71. Found: C=56.23, H=5.02, Cl=8.14, N=15.84, O=3.26, S=7.12.

**N-4-Aminophenyl-[(3-dimethylaminomethyl-indol-1-yl)acetyl]-hydrazinecarbothioamide (4f)**

Gray solid, yield: 75%, mp: 151-153 °C; IR (KBr): 3368 (N-H), 3038 (C-H, Ar), 2962 (C-H, CH_{3}), 1670 (C=O), 1572 (C=C, Ar), 1367 (C=S) cm^{-1}; \(^1\)H NMR (300 MHz, DMSO-d_{6}): δ 11.07 (s, 1H, NH), 9.35 (s, 1H, CSNH), 9.24 (s, 1H, CONH), 7.75-7.26 (m, 4H, Ar-H), 7.55 (d, 2H, J = 7.3 Hz, CH), 7.39 (d, 2H, J = 7.3 Hz, Ar-H), 7.27 (s, 1H, CH), 4.23 (s, 2H, NH_{2}), 3.26 (s, 2H, COCH_{2}), 2.34 (s, 2H, NCH_{2}), 1.25 (s, 6H, 2XCH_{3}); \(^{13}\)C NMR (100 MHz, DMSO-d_{6}): δ 173.6, 170.4, 145.2, 141.5, 134.5, 127.7, 126.6, 123.0, 122.4, 121.1, 117.6, 115.4, 113.6, 112.7, 66.3, 54.8, 46.3; MS: 396 m/z (M^+); Elemental analysis: Calculated for C_{20}H_{24}N_{5}OS: C=60.58, H=6.10, N=21.20, O=4.04, S=8.09. Found: C=59.62, H=5.85, N=20.23, O=3.95, S=7.85.

**5-(3-Dimethylaminomethyl-indol-1-ylmethyl)-4-phenyl-4H-[1,2,4]triazole-3-thiol (5a)**

Orange solid, yield: 74%, mp: 141-143 °C; IR (KBr): 3034 (C-H, Ar), 2962 (C-H, CH_{3}), 2564 (S-H), 1586 (C=C, Ar), 1446 (C=N) cm^{-1}; \(^1\)H NMR (300 MHz, DMSO-d_{6}): δ 7.78-7.20 (m, 9H, Ar-H), 7.34 (s, 1H, CH), 3.74 (s, 1H, SH), 3.35 (s, 2H, CH_{2}), 2.28 (s, 2H, NCH_{2}), 1.21 (s, 6H, 2XCH_{3}); \(^{13}\)C NMR (100 MHz, DMSO-d_{6}): δ 162.2, 148.8, 142.6, 136.5, 129.6, 127.5, 125.4, 123.4, 122.0, 121.6, 120.1, 119.6, 117.6, 114.3, 61.2, 51.6, 40.3; MS: 363 m/z (M^+); Elemental analysis: Calculated for C_{20}H_{21}N_{5}S: C=66.09, H=5.82, N=19.27, S=8.82. Found: C=65.12, H=5.08, N=18.45, S=8.09.
5-(3-Dimethylaminomethyl-indol-1-ylmethyl)-4-o-toly-4H-[1,2,4]triazole-3-thiol (5b)

Brown solid, yield: 74%, mp: 128-130 °C; IR (KBr): 3032 (C-H, Ar), 2970 (C-H, CH₃), 2558 (S-H), 1592 (C=C, Ar), 1454 (C=N) cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆): δ 7.70-7.26 (m, 8H, Ar-H), 7.36 (s, 1H, CH), 3.74 (s, 1H, SH), 3.36 (2H, CH₂), 2.28 (s, 2H, NCH₂), 2.20 (s, 3H, CH₃), 1.32 (s, 6H, 2XCH₃); ¹³C NMR (100 MHz, DMSO-d₆): δ 168.7, 145.6, 142.8, 137.5, 133.6, 129.4, 128.4, 125.1, 125.1, 124.1, 122.7, 121.3, 120.5, 117.6, 114.8, 112.3, 58.3, 46.3, 44.5, 21.3; MS: 377 m/z (M⁺); Elemental analysis: Calculated for C₂₁H₂₃N₅S: C-66.81, H-6.14, N-18.55, S-8.49. Found: C-65.66, H-5.85, N-17.89, S-8.02.

2-[3-(3-Dimethylaminomethyl-indol-1-ylmethyl)-5-mercapto-[1,2,4]triazol-4-yl]-phenol (5c)

White solid, yield: 70%, mp: 113-115 °C; IR (KBr): 3245 (O-H), 3064 (C-H, Ar), 2971 (C-H, CH₃), 2598 (S-H), 1582 (C=C, Ar), 1461 (C=N) cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆): δ 11.19 (s, 1H, O-H), 7.71-7.23 (m, 8H, Ar-H), 7.31 (s, 1H, CH), 3.87 (s, 1H, SH), 3.22 (s, 2H, CH₂), 2.35 (s, 2H, NCH₂), 1.31 (s, 6H, 2XCH₃); ¹³C NMR (100 MHz, DMSO-d₆): δ 163.7, 152.3, 148.5, 145.2, 136.8, 131.2, 130.8, 128.6, 124.1, 121.1, 120.9, 117.5, 115.2, 114.2, 112.0, 111.7, 59.6, 48.7, 42.5; MS: 379 m/z (M⁺); Elemental analysis: Calculated for C₂₀H₂₁N₂OS: C-63.30, H-5.58, N-18.46, O-4.22, S-8.45. Found: C-62.25, H-5.12, N-17.84, O-4.02, S-7.89.

5-(3-Dimethylaminomethyl-indol-1-ylmethyl)-4-(4-methoxy-phenyl)-4H-[1,2,4]triazole-3-thiol (5d)

Gray solid, yield: 70%, mp: 160-162 °C; IR (KBr): 3054 (C-H, Ar), 2974 (C-H, CH₃), 2578 (S-H), 1588 (C=C, Ar), 1465 (C=N), 1149 (C-O) cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆): δ 7.79-7.21 (m, 4H, Ar-H), 7.58 (d, 2H, J = 7.0 Hz, Ar-H), 7.41 (d, 2H, J = 7.0 Hz, CH), 7.33 (s, 1H, CH), 3.78 (s, 1H, SH), 3.45 (s, 2H, CH₂), 2.42 (s, 2H, NCH₂), 2.31 (s, 3H, CH₃), 1.42 (s, 6H, 2XCH₃); ¹³C NMR (100 MHz, DMSO-d₆): δ 163.3, 161.2, 148.6, 146.2, 137.5, 136.4, 125.6, 124.3, 123.5, 121.5, 117.4, 116.3, 113.2, 110.8, 62.3, 58.5, 51.4, 45.8; MS: 265 m/z (M⁺); Elemental analysis: Calculated for C₂₁H₂₃N₅OS: C-64.10, H-5.89, N-17.80, O-4.07, S-8.15. Found: C-63.21, H-5.12, N-16.98, O-3.89, S-7.84.

4-(4-Chloro-phenyl)-5-(3-dimethylaminomethyl-indol-1-ylmethyl)-4H-[1,2,4]triazole-3-thiol (5e)

Pale yellow solid, yield: 74%, mp: 123-125 °C; IR (KBr): 3063 (C-H, Ar), 2970 (C-H, CH₃), 2574 (S-H), 1565 (C=C, Ar), 1462 (C=N) cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆): δ 7.81-7.26
(m, 4H, Ar-H), 7.60 (d, 2H, J = 7.0 Hz, CH), 7.41 (d, 2H, J = 7.0 Hz, Ar-H), 7.31 (s, 1H, CH), 3.81 (s, 1H, SH), 3.32 (s, 2H, CH₂), 2.41 (s, 2H, NCH₂), 1.36 (s, 6H, 2XCH₃); ¹³C NMR (100 MHz, DMSO-d₆): δ 162.8, 144.6, 142.6, 137.4, 132.6, 129.7, 127.5, 126.4, 125.7, 120.7, 119.4, 116.2, 112.4, 56.3, 52.3, 46.3; MS: 397 m/z (M⁺); Elemental analysis: Calculated for C₂₀H₂₀ClN₅S: C - 60.37, H - 5.07, Cl - 8.91, N - 17.06, S - 8.06. Found: C - 59.02, H - 4.85, Cl - 8.03, N - 16.28, S - 7.86.

4-(4-Amino-phenyl)-5-(3-dimethylaminomethyl-indol-1-ylmethyl)-4H-[1,2,4]triazole-3-thiol (5f)

Brown solid, yield: 77%, mp: 120-122 °C; IR (KBr): 3358 (N-H), 3062 (C=H, Ar), 1612 (C=O), 1458 (C=N) cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆): δ 7.78-7.25 (m, 4H, Ar-H), 7.61 (d, 2H, J = 7.3 Hz, CH), 7.38 (d, 2H, J = 7.3 Hz, Ar-H), 7.31 (s, 1H, CH), 4.24 (s, 2H, NH₂), 3.84 (s, 1H, SH), 3.28 (s, 2H, CH₂), 2.29 (s, 2H, NCH₂), 1.36 (s, 6H, 2XCH₃); ¹³C NMR (100 MHz, DMSO-d₆): δ 163.2, 146.8, 143.5, 141.0, 136.2, 128.1, 126.5, 124.1, 123.9, 118.6, 116.5, 115.2, 114.2, 112.4, 56.8, 52.0, 43.2; MS: 378 m/z (M⁺); Elemental analysis: Calculated for C₂₀H₂₂N₆S: C - 63.47, H - 5.86, N - 22.20, S - 7.98. Found: C - 62.65, H - 5.12, N - 21.45, S - 7.98.

REFERENCES