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Synthesis of new pyrimidinylthio-substituted 1,3,4-oxa(thia)diazoles and 1,2,4-triazoles

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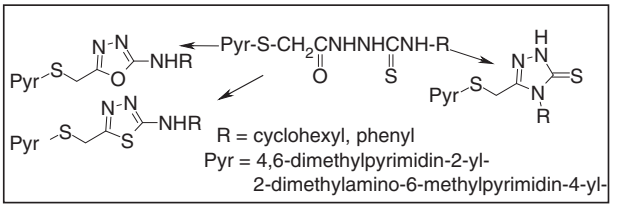
Novel 1,3,4-oxadiazoles, 1,3,4-thiadiazoles and 1,2,4-triazole-3-thiones bearing the pyrimidinylthio-moiety were synthesized by cyclization of a substituted-thiosemicarbazide precursor under different conditions. The thiosemicarbazide intermediates were easily accessed from reaction of biologically active 2-(4,6-dimethylpyrimidin-2-ylthio)acetohydrazide and 2-(2-dimethylamino-6-methyl pyrimidin-4-ylthio)acetohydrazide with cyclohexyl or phenyl isothiocyanate. The compounds are characterized by ^{1}H, ^{13}C NMR, IR spectroscopy and analytical data.



Keywords: pyrimidine; thiosemicarbazide; 1,3,4-oxadiazole, 1,3,4-thiadiazole, 1,2,4-triazole

1. Introduction

Heterocyclic compounds form the basis of pharmaceutical and agrochemical products. Azoles including 1,2,4-triazoles, 1,3,4-oxadiazoles and 1,3,4-thiadiazoles are in particular an important class of compounds of considerable biological and technological interest that are appearing in an increasing number of publications. These azoles potentially possess a variety of valuable properties including antitubercular (*1*, *2*), antimicrobial (*2–8*), anticancer (*9–11*), anti-inflammatory, analgetic (*12*, *13*), antibacterial (*14*, *15*), anticonvulsant (*16*, *17*) and tyrosinase (*18*) or monoamine oxidase (*19*) inhibitory activity. 1,3,4-Oxadiazoles are also extensively investigated as promising materials for application in electronic technologies as photosensitizers, liquid crystals and organic

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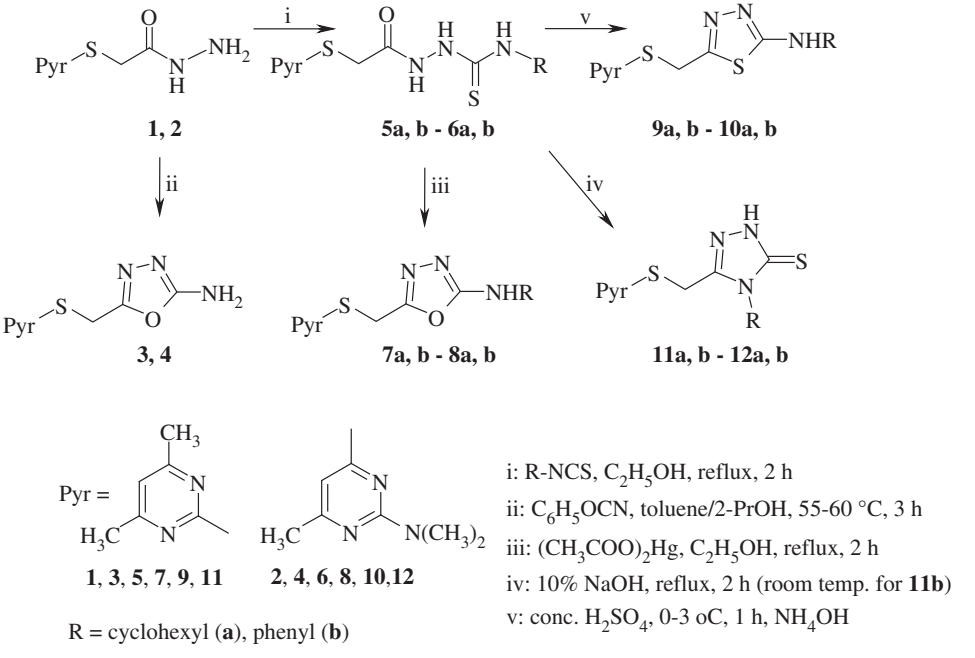
light emitting diodes (*20–22*). The synthetic approaches to these heterocycles therefore are widely reported and are receiving considerable attention. Several review articles have been published that discuss the most frequently used, as well as uncommon synthetic methods, for the synthesis of 1,2,4-triazoles and 1,3,4-oxa(thia)diazoles (*1*, *23–31*). An excellent strategy for the synthesis of these azoles is the cyclization of substituted thiosemicarbazides, respectively (*8*, *32*, *33*).

As a continuation of our research in the synthesis of new heterocycles of potential biological importance, we report here the synthesis of substituted (2-pyrimidinyl)- and (4-pyrimidinyl)thiosemicarbazides and their cyclization products. Our interest was to develop efficient procedures for the synthesis of novel 1,3,4-oxadiazoles, 1,3,4-thiadiazoles and 1,2,4-triazoles linked by sulfur to a pyrimidine moiety.

2. Results and discussion

Biologically active hydrazides **1** and **2** were used for the synthesis of azoles. (4,6-Dimethylpyrimidin-2-ylthio)acethydrazide (**1**) and its derivatives were previously found to inhibit monoamino oxidase activity (*34*), while derivatives of (2-dimethylamino-6-methylpyrimidin-4-ylthio)acethydrazide (**2**) showed anti-inflammatory activity (*35*). In this context, it was worthwhile to utilize these hydrazides for the synthesis of new potentially active biologically heterocyclic systems.

Substituted thiosemicarbazides **5a** and **b** and **6a** and **b** were readily prepared by acylation of hydrazides **1** and **2** in absolute ethanol with cyclohexyl or phenyl isothiocyanate as shown in Scheme 1. Compounds **5** and **6** precipitated from the reactions mixtures in good yield as white solids of excellent purity. The ^{1}H NMR spectra of thiosemicarbazides **5** and **6** displayed three sets of singlets between 6.48 and 10.27 ppm due to three NH group protons. The pyrimidine 5-CH



Scheme 1. Reagents and reaction conditions for the synthesis of compounds **3–12**.

singlet was observed between 6.37 and 6.98 ppm and the SCH_2 group protons between 3.86 and 3.99 ppm. In addition, the signals for the cyclohexyl and phenyl group protons as well as the pyrimidine ring substituents (CH_3 and $N(CH_3)_2$) were compatible with structures **5** and **6**. The IR spectra displayed characteristic carbonyl frequencies at 1702–1662 cm^{-1} and NH bands at 3336–3140 cm^{-1}.

Thiosemicarbazides **5** and **6** can be cyclized under different conditions to the corresponding azoles. The cyclodesulfurization to form 1,3,4-oxadiazoles have been conducted by treating thiosemicarbazides with iodine in the presence of a base (*32*), either with mercury (II) hydroxide (*36*) or acetate (*32*, *37*). For the synthesis of oxadiazoles **7** and **8**, several attempts were made to ascertain the optimal reaction conditions. It was found that the use of mercury (II) acetate provided shorter reaction time, simple work-up procedure and yields comparable to the other procedures. Thus, compounds **5** and **6** were heated at reflux in ethanol in the presence of mercury (II) acetate for 2 h. After filtration of by-products and concentration of the solvent, the 2-amino-substituted 1,3,4-oxadiazoles **7** and **8** crystallized in 75–88% yield. Treatment of the starting hydrazides **1** and **2** with phenyl cyanate at 55–60°C in anhydrous conditions in a mixture of toluene and 2-propanol gave the 2-amino-1,3,4-oxadiazoles **3** and **4** directly.

2-Amino-substituted 1,3,4-thiadiazoles **9** and **10** were synthesized by cyclodehydration reactions of **5** and **6** in acidic media. Thiosemicarbazides **5** and **6** were treated with concentrated sulfuric acid at $\sim$ 0°C and upon neutralization of the reaction mixture with ammonium hydroxide the products **9** and **10** were isolated as white solids in 52–65% yield. The structural assignments for **3**, **4** and **7**–**10** were made by examination of IR and NMR data. In the IR spectra of compounds **3**, **4** and **7**–**10**, absorption bands at 1609–1500 cm^{-1} were observed for C=N and C=C and between 3303 and 3120 cm^{-1} for the NH and NH_2 groups. Compounds **3** and **4** also displayed peaks at 1664–1663 cm^{-1} arising from bending vibrations of the N−H bonds. Noteworthy in the ^1H NMR spectra, the SCH_2 singlets were shifted downfield by at least 0.5 ppm in comparison to the shifts observed in the starting compounds **5** and **6**. The NH protons for the compounds with the cyclohexyl substituent (**7a**, **8a**, **9a** and **10a**) appeared as doublets at 7.51–7.55 ppm, while those with the phenyl group (**7b**, **8b**, **9b** and **10b**) displayed singlets at 10.24–10.48 ppm.

Thiosemicarbazides **5** and **6** on treatment with aqueous sodium hydroxide undergo smooth cyclodehydration to give 1,2,4-triazoles **11** and **12** in 87–95% yields. Conversion of **5b** to **11b** occurred at room temperature while the other compounds required heating of the reaction mixtures at reflux. The IR spectra of triazole-3-thiones **11** and **12** displayed absorption bands at 3091–3099 cm^{-1} for NH. The stretchings at 1585–1551, 1501–1494 cm^{-1} are attributable to the C=N and C=C bonds and the absorptions at 1342–1331 cm^{-1} arise from C=S vibrations. The characteristic triazole NH proton singlet appeared in the ^1H NMR spectra in the downfield between 13.10 and 13.86 ppm and the SCH_2 singlets upfield between 4.34 and 4.49 ppm. The chemical shifts of the pyrimidine and triazole ring substituents are also consistent with their structures.

3. Conclusions

We have developed concise and efficient procedures for the synthesis of novel 1,3,4-oxadiazoles, 1,3,4-thiadiazoles and 1,2,4-triazoles bearing 4-pyrimidinylthio- and 2-pyrimidinylthio moieties. The target compounds were obtained from the acylation reaction of biologically active (2-dimethylamino-6-methylpyrimidin-4-ylthio)acetohydrazide and (4,6-dimethylpyrimidin-2-ylthio)acetohydrazide with isothiocyanates followed by intramolecular cyclization of substituted thiosemicarbazides intermediates. All the compounds prepared are under evaluation for their antimicrobial activity and the results will be published later.

4. Experimental

Melting points were determined in open capillaries using digital melting point IA9100 series apparatus (Fisher Scientific) and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Unity Varian INOVA spectrometer (300 and 75 MHz, respectively) using residual solvents signals as the internal standard. The IR spectra were recorded on a Spectrum BX FT-IR (Perkin-Elmer) in KBr discs. The reactions and purities of the compounds were monitored by TLC on Silica gel 60 F254 aluminum plates (Merck). Visualization was accomplished by UV light. Elemental analyses were performed at the Microanalyses Laboratory of the Department. Reagents and solvents were purchased from commercial sources.

2-(4,6-Dimethylpyrimidin-2-ylthio)acetohydrazide (**1**) and (2-dimethylamino-6-methyl-pyrimidin-4-ylthio)acetohydrazide (**2**) were synthesized as earlier reported (*34*, *35*).

4.1. *Synthesis of 2-amino-1,3,4-oxadiazoles 3 and 4*

Hydrazide **1** or **2** (5 mmol) was suspended in a mixture of dry toluene (10 ml) and 2-propanol (4 ml). Phenyl cyanate (0.61 g, 0.56 ml, 5.1 mmol) was added dropwise to this suspension and the reaction mixture was stirred at 55–60°C for 3 h. The precipitate was filtered, washed with ethanol and ether, dried and recrystallized from 2-ethoxyethanol to give colorless crystals of **3** or **4**.

4.1.1. *2-Amino-5-[(4,6-dimethylpyrimidin-2-ylthio)methyl]-1,3,4-oxadiazole (3)*

Yield 65%, mp 219–220°C. IR, ν, cm^{-1}: 3332, 3228, 1663 (NH_2), 1578, 1535 (C=N, C=C). ^{1}H NMR (DMSO-d_6) δ: 2.37 (s, 6H, CH_3), 4.49 (s, 2H, SCH_2), 7.03 (s br, 3H, CH-pyrimidine + NH_2); ^{13}C NMR (DMSO-d_6) δ: 24.03, 24.42, 117.23, 157.08, 164.61, 168.06, 168.47. Anal. calcd. for $C_9H_{11}N_5OS$ (237.28): C, 45.56; H, 4.67; N, 29.51%. Found: C, 45.37; H, 4.70; N, 29.45%.

4.1.2. *2-Amino-5-[(2-dimethylamino-6-methylpyrimidin-4-ylthio)methyl]-1,3,4-oxadiazole (4)*

Yield 70%, mp 193–194°C. IR, ν, cm^{-1}: 3302, 3118, 1664 (NH_2), 1573, 1552 (C=N, C=C). ^{1}H NMR (DMSO-d_6) δ: 2.20 (s, 6H, CH_3), 3.11 (s, 6H, $N(CH_3)_2$), 4.49 (s, 2H, SCH_2), 6.47 (s, 1H, CH-pyrimidine), 7.03 (s, 2H, NH_2); ^{13}C NMR (DMSO-d_6) δ: 22.46, 24.31, 105.76, 157.08, 161.37, 164.58, 166.38, 166.67. Anal. calcd. for $C_{10}H_{14}N_6OS$ (266.32): C, 45.10; H, 5.30; N, 31.56%. Found: C, 45.15; H, 5.13; N, 31.61%.

4.2. *Synthesis of substituted thiosemicarbazides 5a and b and 6a and b*

Hydrazide **1** or **2** (5 mmol) was dissolved in abs. ethanol (~30 ml) and cyclohexyl (or phenyl) isothiocyanate (5.5 mmol) was added. The reaction mixture was stirred at reflux for 2 h and cooled. The resultant solid was filtered off, dried and recrystallized.

4.2.1. *4-Cyclohexyl-1-[(4,6-dimethylpyrimidin-2-ylthio)acetyl]thiosemicarbazide (**5a**)*

Yield 74% (2-propanol), mp 156–158°C (acetone–water). IR, ν, cm^{-1}: 3296, 3238 (NH), 1686 (C=O), 1584, 1546 (C=N, C=C), 1341 (C=S). ^{1}H NMR ($CDCl_3$) δ: 1.17–1.26, 1.37–1.41, 1.67–1.79, 1.98–2.01 (4m, 10H, CH_2-cyclohexyl), 2.51 (s, 6H, CH_3), 3.86 (s, 2H, SCH_2), 4.03–4.07 (m, 1H, CH-cyclohexyl), 6.82 (s, 1H, CH-pyrimidine), 6.94 (s br, 1H, CSN*H*), 9.31 (s br, 1H, N*H*CS), 10.19 (s br, 1H, CON*H*); ^{13}C NMR ($CDCl_3$) δ: 24.28, 24.86, 25.61, 25.71, 32.75, 53.27,

117.13, 166.29, 168.30, 169.45, 178.63. Anal. calcd. for $C_{15}H_{23}N_5OS_2$ (353.51): C, 50.96; H, 6.56; N, 19.81%. Found: C, 51.11; H, 6.58; N, 19.93%.

4.2.2. *1-[(4,6-Dimethylpyrimidin-2-ylthio)acetyl]-4-phenylthiosemicarbazide (**5b**)*

Yield 91% (ethanol–acetone), mp 175–176°C. IR, ν, cm^{-1}: 3270, 3210 (NH), 1662 (C=O), 1584, 1561, 1498 (C=C, C=N), 1340 (C=S). ^{1}H NMR (DMSO-d_6) δ: 2.36 (s, 6H, CH_3), 3.99 (s, 2H, SCH_2), 6.98 (s, 1H, CH-pyrimidine), 7.16–7.21 (m, 1H, Ph-H), 7.32–7.42 (m, 4H, Ph-H), 9.59 (s br, 1H, CSN*H*), 9.74 (s br, 1H, N*H*CS), 10.27 (s br, 1H, CON*H*); ^{13}C NMR (DMSO-d_6) δ: 24.05, 33.60, 116.86, 125.88, 126.59, 128.83, 139.68, 167.85, 168.30, 169.78, 181.49. Anal. calcd. for $C_{15}H_{17}N_5OS_2$ (347.46): C, 51.85; H, 4.93; N, 20.16%. Found: C, 51.66; H, 5.01; N, 20.24%.

4.2.3. *4-Cyclohexyl-1-[(2-dimethylamino-6-methylpyrimidin-4-ylthio)acetyl] thiosemicarbazide (**6a**)*

Yield 88%, mp 178–180°C (ethanol). IR, ν, cm^{-1}: 3306, 3140 (NH), 1701 (C=O), 1580, 1548 (C=N, C=C), 1315 (C=S). ^{1}H NMR ($CDCl_3$) δ: 1.02–1.20, 1.32–1.43, 1.59–1.69, 1.93–1.96 (4m, 10H, CH_2-cyclohexyl), 2.30 (s, 3H, CH_3), 3.20 (s, 6H, $N(CH_3)_2$), 3.87 (s, 2H, SCH_2), 4.09–4.12 (m, 1H, CH-cyclohexyl), 6.37 (s, 1H, CH-pyrimidine), 6.48 (s br, 1H, CSN*H*), 8.48 (s br, 1H, N*H*CS), 9.64 (s br, 1H, CON*H*); ^{13}C NMR ($CDCl_3$) δ: 24.35, 24.87, 25.65, 31.17, 32.52, 37.49, 53.36, 106.07, 161.74, 165.83, 167.07, 168.09, 180.23. Anal. calcd. for $C_{16}H_{26}N_6OS_2$ (382.55): C, 50.23; H, 6.85; N, 21.97%. Found: C, 50.09; H, 6.88; N, 22.09%.

4.2.4. *1-[(2-Dimethylamino-6-methylpyrimidin-4-ylthio)acetyl]-4-phenylthiosemicarbazide (**6b**)*

Yield 73%, mp 165–167°C. IR, ν, cm^{-1}: 3336, 3142 (NH), 1686 (C=O), 1605, 1560, 1498 (C=N, C=C), 1317 (C=S). ^{1}H NMR (DMSO-d_6) δ: 2.20 (s, 3H, CH_3), 3.08 (s, 6H, $N(CH_3)_2$), 3.99 (s, 2H, SCH_2), 6.46 (s, 1H, CH-pyrimidine), 7.18–7.20 (m, 1H, Ph-H), 7.32–7.37 (m, 4H, Ph-H), 9.50 (s br, 1H, CSN*H*), 9.73 (s br, 1H, N*H*CS), 10.23 (s br, 1H, CON*H*); ^{13}C NMR (DMSO-d_6) δ: 24.35, 31.63, 37.23, 105.68, 125.90, 126.9, 126.43, 128.85, 139.65, 161.55, 166.15, 167.87, 181.55. Anal. calcd. for $C_{16}H_{20}N_6OS_2$ (376.50): C, 51.04; H, 5.35; N, 22.32%. Found: C, 51.16; H, 5.41; N, 22.33%.

4.3. *Synthesis of 1,3,4-oxadiazoles 7a and b and 8a and b*

To a stirred solution of thiosemicarbazide **5** or **6** (1 mmol) in ethanol (15 ml), mercury (II) acetate (0.32 g, 1 mmol) was added in portion. The reaction mixture was heated at reflux for 2 h and filtered. The filtrate was concentrated, cooled and the precipitate formed was collected by filtration and recrystallized.

4.3.1. *2-Cyclohexylamino-5-[(4,6-dimethylpyrimidin-2-ylthio)methyl]-1,3,4-oxadiazole (**7a**)*

Yield 75%, mp 191–192°C (ethyl acetate). IR, ν, cm^{-1}: 3189 (NH), 1604, 1584 (C=N, C=C). ^{1}H NMR (DMSO-d_6) δ: 1.18–1.28, 1.51–1.60, 1.65–1.73, 1.87–1.89 (4m, 10H, CH_2-cyclohexyl), 2.37 (s, 6H, CH_3), 3.25–3.36 (m, 1H, CH-cyclohexyl), 4.50 (s, 2H, SCH_2), 7.03 (s, 1H, CH-pyrimidine), 7.52 (d, $J = 7.5$ Hz, 1H, NH); ^{13}C NMR (DMSO-d_6) δ: 24.03, 24.42, 25.05, 25.83, 32.89, 52.41, 117.23, 157.05, 163.64, 168.04, 168.45. Anal. calcd. for $C_{15}H_{21}N_5OS$ (319.43): C, 56.40; H, 6.63; N, 21.92%. Found: C, 56.46; H, 6.51; N, 21.89%.

4.3.2. *5-[(4,6-Dimethylpyrimidin-2-ylthio)methyl]-2-phenylamino-1,3,4-oxadiazole (7b)*

Yield 76%, mp 166–168°C (benzene). IR, ν, cm^{-1}: 3178, (NH), 1602, 1578, 1504 (C=N, C=C). ^1H NMR (DMSO-d_6) δ: 2.39 (s, 6H, CH_3), 4.63 (s, 2H, SCH_2), 7.06 (s, 1H, CH-pyrimidine), 7.0 (t, $J = 8$ Hz, 1H, Ph-H), 7.33 (t, $J = 8$ Hz, 2H, Ph-H), 7.52 (d, $J = 8$ Hz, 2H, Ph-H), 10.48 (s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ: 24.06, 24.39, 117.30, 117.57, 122.48, 129.75, 139.36, 157.94, 160.67, 168.11, 168.42. Anal. calcd. for $C_{15}H_{15}N_5OS$ (313.38): C, 57.49; H, 4.82; N, 22.35%. Found: C, 57.59; H, 4.67; N, 22.49%.

4.3.3. *2-Cyclohexylamino-5-[(2-dimethylamino-6-methylpyrimidin-4-ylthio)methyl]-1,3,4-oxadiazole (**8a**)*

Yield 76%, mp 144–146°C. IR, ν, cm^{-1}: 3241 (NH), 1580, 1555 (C=N, C=C). ^1H NMR (DMSO-d_6) δ: 1.18–1.28, 1.52–1.60, 1.62–1.72, 1.90–1.94 (4m, 10H, CH_2-cyclohexyl), 2.20 (s, 1H, CH_3), 3.11 (s, 6H, $N(CH_3)_2$), 3.30–3.40 (m, 1H, CH-cyclohexyl), 4.50 (s, 2H, SCH_2), 6.48 (s, 1H, CH-pyrimidine), 7.49 (d, $J = 7.5$ Hz, 1H, NH); ^{13}C NMR (DMSO-d_6) δ: 22.46, 24.37, 25.07, 25.86, 32.91, 37.22, 52.43, 105.80, 157.11, 161.53, 163.69, 166.52. Anal. calcd. for $C_{16}H_{24}N_6OS$ (348.47): C, 55.15; H, 6.94; N, 24.12%. Found: C, 55.37; H, 6.79; N, 24.14%.

4.3.4. *5-[(2-Dimethylamino-6-methylpyrimidin-4-ylthio)methyl]-2-phenylamino-1,3,4-oxadiazole (**8b**)*

Yield 88%, mp 194–195°C. IR, ν, cm^{-1}: 3248 (NH), 1571, 1550, 1500 (C=N, C=). ^1H NMR (DMSO-d_6) δ: 2.21 (s, 1H, CH_3), 3.11 (s, 6H, $N(CH_3)_2$), 4.62 (s, 2H, SCH_2), 6.51 (s, 1H, CH-pyrimidine), 6.99 (t, $J = 8$ Hz, 1H, Ph-H), 7.32 (t, $J = 8$ Hz, 2H, Ph-H), 7.50 (d, $J = 8$ Hz, 2H, Ph-H), 10.46 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ: 22.43, 24.32, 37.25, 105.83, 117.59, 122.48, 129.74, 139.34, 157.99, 160.64, 161.44, 162.28, 166.49. Anal. calcd. for $C_{16}H_{18}N_6OS$ (342.42): C, 56.12; H, 5.30; N, 24.54%. Found: C, 56.07; H, 5.17; N, 24.48%.

4.4. *Synthesis of 1,3,4-thiadiazoles 9a and b and 10a and b*

Thiosemicarbazide **5** or **6** (1 mmol) was added gradually with stirring to conc. sulfuric acid (5 ml) at 0–3°C. The reaction mixture was then stirred for 2 h at room temperature, poured over crushed ice and neutralized with ammonium hydroxide to pH $\sim$ 7. The precipitate thus formed was filtered off, washed with water, dried and recrystallized.

4.4.1. *2-Cyclohexylamino-5-[(4,6-dimethylpyrimidin-2-ylthio)methyl]-1,3,4-thiadiazole (**9a**)*

Yield 65%, mp 185–187°C (2-propanol). IR, ν, cm^{-1}: 3185 (NH), 1586, 1520 (C=N, C=C). ^1H NMR (DMSO-d_6) δ: 1.17–1.27, 1.52–1.60, 1.62–1.67, 1.91–1.94 (4m, 10H, CH_2-cyclohexyl), 2.40 (s, 6H, CH_3), 3.50 (s br, 1H, CH-cyclohexyl), 4.52 (s, 2H, SCH_2), 7.05 (s, 1H, CH-pyrimidine), 7.54 (d, $J = 7.2$ Hz, 1H, NH); ^{13}C NMR (DMSO-d_6) δ: 23.97, 24.92, 25.94, 29.63, 32.74, 53.88, 117.15, 155.22, 168.08, 169.01, 169.07. Anal. calcd. for $C_{15}H_{21}N_5S_2$ (335.49): C, 53.70; H, 6.31; N, 20.87%. Found: C, 53.79; H, 6.27; N, 20.64%.

4.4.2. *5-[(4,6-Dimethylpyrimidin-2-ylthio)methyl]-2-phenylamino-1,3,4-thiadiazole (**9b**)*

Yield 62%, mp 196–197°C (2-propanol). IR, ν, cm^{-1}: 3261 (NH), 1609, 1578, 1556, 1508 (C=N, C=C). ^1H NMR (DMSO-d_6) δ: 2.42 (s, 6H, CH_3), 4.63 (s, 2H, SCH_2), 6.99 (t, $J = 8$ Hz, 1H, Ph-H), 7.07 (s, 1H, CH-pyrimidine), 7.33 (t, $J = 8$ Hz, 2H, Ph-H), 7.57–7.60 (m, 2H, Ph-H), 10.24 (s,

1H, NH); ^{13}C NMR (DMSO-d_6) δ: 23.98, 29.51, 117.26, 118.03, 122.48, 129.77, 141.29, 157.81, 165.70, 168.17, 168.95. Anal. calcd. for $C_{15}H_{15}N_5S_2$ (329.45): C, 54.69; H, 4.59; N, 21.26%. Found: C, 54.78; H, 4.66; N, 21.48%.

4.4.3. *2-Cyclohexylamino-5-[(2-dimethylamino-6-methylpyrimidin-4-ylthio)methyl]-1,3,4-thiadiazole (**10a**)*

Yield 52%, mp 203–205°C (ethanol). IR, ν, cm^{-1}: 3307 (NH), 1547, 1519 (C=N, C=C). ^{1}H NMR (DMSO-d_6) δ: 1.18–1.28, 1.54–1.58, 1.60–1.70, 1.90–1.94 (4m, 10H, CH_2-cyclohexyl), 2.21 (s, 1H, CH_3), 3.15 (s, 6H, $N(CH_3)_2$), 3.47 (s br, 1H, CH-cyclohexyl), 4.59 (s, 2H, SCH_2), 6.47 (s, 1H, CH-pyrimidine), 7.54 (d, $J = 7.2$ Hz, 1H, NH); ^{13}C NMR (DMSO-d_6) δ: 24.37, 24.92, 25.96, 27.46, 32.74, 37.31, 53.83, 106.09, 155.82, 161.53, 166.55, 166.75, 168.92. Anal. calcd. for $C_{16}H_{24}N_6S_2$ (364.53): C, 52.72; H, 6.64; N, 23.05%. Found: C, 52.67; H, 6.70; N, 23.15%.

4.4.4. *5-[(2-Dimethylamino-6-methylpyrimidin-4-ylthio)methyl]-2-phenylamino-1,3,4-thiadiazole (**10b**)*

Yield 59%, mp 193–195°C (ethyl acetate). IR, ν, cm^{-1}: 3280 (NH), 1606, 1547, 1507 (C=N, C=C). ^{1}H NMR (DMSO-d_6) δ: 2.23 (s, 6H, CH_3), 3.17 (s, 6H, $N(CH_3)_2$), 4.70 (s, 2H, SCH_2), 6.54 (s, 1H, CH-pyrimidine), 6.99 (t, $J = 8$ Hz, 1H, Ph-H), 7.35 (t, $J = 8.4$ Hz, 2H, Ph-H), 7.59 (d, $J = 8.4$ Hz, 2H, Ph-H), 10.25 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ: 28.76, 32.19, 42.24, 110.96, 118.03, 122.76, 127.23, 134.52, 145.98, 156.99, 163.14, 165.62, 170.31, 170.65, 172.08. Anal. calcd. for $C_{16}H_{18}N_6S_2$ (358.49): C, 53.61; H, 5.06; N, 23.44%. Found: C, 53.87; H, 4.93; N, 23.53%.

4.5. *Synthesis of 1,2,4-triazole-3(4H)-thiones 11a and b and 12a and b*

Thiosemicarbazide **5** or **6** (1 mmol) was suspended in 10% sodium hydroxide solution (10–15 ml) and stirred at room temperature (for **5b**) or heated gently at reflux for 2 h. The cooled mixture was poured over crushed ice and then neutralized with acetic acid to pH 7. The precipitate was filtered off, washed with water and recrystallized.

4.5.1. *4-Cyclohexyl-5-[(4,6-dimethylpyrimidin-2-ylthio)methyl]-2H-1,2,4-triazole-3(4H)-thione (**11a**)*

Yield 95%, mp 212–213°C (methanol). IR, ν, cm^{-1}: 3091 (NH), 1582, 1551, 1494 (C=N, C=C), 1339 (C=S). ^{1}H NMR (DMSO-d_6) δ: 1.16–1.19, 1.59–1.69, 1.76–1.81 (3m, 10H, CH_2-cyclohexyl), 2.38 (s, 6H, CH_3), 4.43 (s br, 1H, CH-cyclohexyl), 4.66 (s, 2H, SCH_2), 7.06 (s, 1H, CH-pyrimidine), 13.60 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ: 24.05, 24.25, 25.47, 26.15, 29.54, 56.77, 117.26, 150.08, 167.19, 168.06, 168.47. Anal. calcd. for $C_{15}H_{21}N_5S_2$ (335.49): C, 53.70; H, 6.31; N, 20.87%. Found: C, 53.61; H, 6.39; N, 20.91%.

4.5.2. *5-[(4,6-Dimethylpyrimidin-2-ylthio)methyl]-4-phenyl-2H-1,2,4-triazole-3(4H)-thione (**11b**)*

Yield 87%, mp 198–201°C (2-propanol). IR, ν, cm^{-1}: 3099 (NH), 1585, 1500 (C=N, C=C), 1332 (C=S). ^{1}H NMR (DMSO-d_6) δ: 2.29 (s, 6H, CH_3), 4.34 (s, 2H, SCH_2), 6.95 (s, 1H, CH-pyrimidine), 7.43–7.53 (m, 5H, Ph-H), 13.86 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ: 23.98, 24.97,

117.09, 129.11, 129.98, 130.19, 134.01, 135.23, 150.31, 167.79, 168.14, 168.82. Anal. calcd. for $C_{15}H_5N_5S_2$ (329.45): C, 54.69; H, 4.59; N, 21.26%. Found: C, 54.53; H, 4.61; N, 20.99%.

4.5.3. *4-Cyclohexyl-5-[(2-dimethylamino-6-methylpyrimidin-4-ylthio)methyl]-2H-1,2,4-triazole-3-(4H)-thione (**12a**)*

Yield 87%, mp 243–246°C (2-propanol). IR, ν, cm^{-1}: 3094 (NH), 1562, 1496 (C=N, C=C), 1342 (C=S). ^{1}H NMR (DMSO-d_6) δ: 1.05–1.15, 1.58–1.60, 1.62–1.78 (3m, 10H, CH_2-cyclohexyl), 2.22 (s, 3H, CH_3), 3.13 (s, 6H, $N(CH_3)_2$), 4.32 (s br, 1H, CH-cyclohexyl), 4.69 (s, 2H, SCH_2), 6.50 (s, 1H, CH-pyrimidine), 13.58 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ: 22.99, 24.37, 25.25, 26.09, 29.25, 37.25, 56.93, 106.01, 149.91, 161.47, 166.15, 166.77, 167.19. Anal. calcd. for $C_{16}H_{24}N_6S_2$ (364.53): C, 52.72; H, 6.64; N, 23.05%. Found: C, 52.55; H, 6.88; N, 22.89%.

4.5.4. *5-[(2-Dimethylamino-6-methylpyrimidin-4-ylthio)methyl]-4-phenyl-2H-1,2,4-triazole-3-(4H)-thione (**12b**)*

Yield 88%, mp 205–206°C (2-propanol). IR, ν, cm^{-1}: 3099 (NH), 1560, 1501 (C=N, C=C), 1331 (C=S). ^{1}H NMR ($CDCl_3$) δ: 2.26 (s, 3H, CH_3), 3.11 (s, 6H, $N(CH_3)_2$), 4.41 (s, 2H, SCH_2), 6.19 (s, 1H, CH-pyrimidine), 7.34–7.36 (m, 3H, Ph-H), 7.47–7.49 (m, 2H, Ph-H), 12.10 (s br, 1H, NH); ^{13}C NMR ($CDCl_3$) δ: 22.30, 24.19, 37.17, 105.78, 128.44, 129.92, 130.32, 133.25, 150.57, 161.26, 165.07, 166.30, 169.33. Anal. calcd. for $C_{16}H_{18}N_6S_2$: 358.49, C, 53.61; H, 5.06; N, 23.44%. Found: C, 53.56; H, 5.11; N, 23.49%.

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