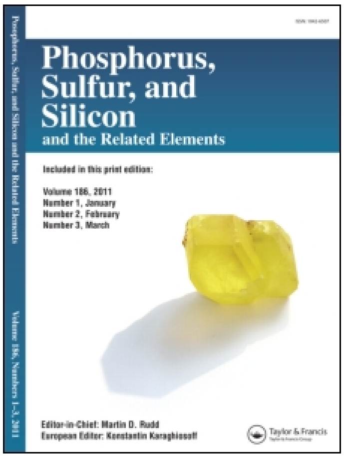

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Synthesis and Characterization of New Thiazolidin-4-one Derivatives

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Synthesis and Characterization of New Thiazolidin-4-one Derivatives

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The synthesis of some new functionalized thiazolidin-4-one derivatives has been described. The N-substituted-thiosemicarbazides ***3a-3i*** *were obtained though the reaction of alkylamines* ***2a–2i****, carbon disulfide, and hydrazine hydrate. The condensation reaction between* ***3a–3i*** *and 4-amino-2-methanesulfanylpyrimidine-5-carboxaldehyde* ***1*** *afforded the thiosemicarbazones* ***4a–4i****. The corresponding thiazolidin-4-ones* ***5a–5i*** *were prepared by cyclization of* ***4a–4i*** *with ethyl bromoacetate. The structures of the final products were confirmed by IR, ^{1}H NMR, ^{13}C NMR, and HRMS.*

Keywords 4-Amino-2-methanesulfanylpyrimidine-5-carboxaldehyde; thiazolidin-4-ones; thiosemicarbazides; thiosemicarbazones

INTRODUCTION

Thiazolidin-4-one derivatives have received much attention due to their widespread application in the chemotherapeutic field. They display a wide variety of biological activities such as antimicobial, antiinflammatory, anti–*Toxoplasma gondii*, and anti-HIV, etc.[1–8] Several synthesis methods for thiazolidin-4-ones have been developed.[9,10] The most important one of them is the cyclization of thiosemicarbazones, which are also of biological interest due to their large spectrum of activity.[11–13]

Pyrimidine heterocycles are structural elements that frequently impart biological activity. However, to our knowledge there is no data describing compounds containing the two heterocyclic moieties,

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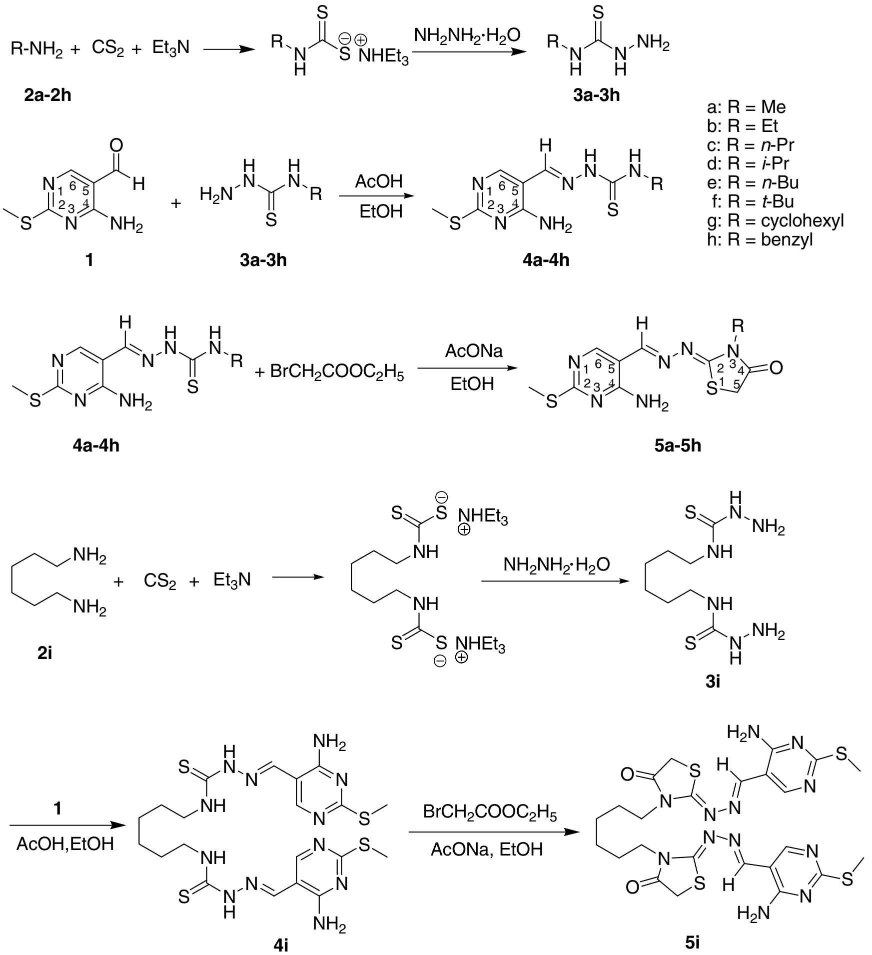
thiazolidin-4-one and pyrimidine. As a part of our research program aimed at synthesizing druglike heterocycles, we became interested in the substituted thiazolidin-4-one containing pyrimidine.

RESULTS AND DISCUSSION

4-Amino-2-methanesulfanylpyrimidine-5-carboxaldehyde **1**, which was prepared by selective oxidation of (4-amino-2-methanesulfanyl pyrimidin-5-yl)methanol using our recently reported method,[14] was selected as the starting material in this work. The N-substituted-thiosemicarbazides **3a–3i** were prepared in a similar method according to the literature.[15,16] In the presence of triethylamine, alkylamines **2a–2i** conveniently react with carbon disulfide to form the intermediate triethylammonium dithiocarbamates, which further reacted with hydrazine hydrate to yield **3a–3i**. The thiosemicarbazones **4a–4i** were synthesized by condensation of **3a–3i** with **1**. The target products, thiazolidin-4-ones **5a–5i**, were synthesized from **4a–4i** by cyclization with ethyl 2-bromoacetate using basic conditions (Scheme 1). Their structures were confirmed by IR, ^{1}H NMR, ^{13}C NMR, and HRMS.

In the procedure for synthesis of N-substituted-thiosemicarbazides**3**, we tested two methods. One method involved the dropwise addition of carbon disulfide into the mixture of alkylamines and triethylamine with stirring, the other was to add the alkylamines dropwise into the mixtures of carbon disulfide and triethylamine. For all the compounds **3a–i**, with the exception of **3h**, essentially the same results were obtained. In the preparation of **3h**, the two methods showed different results: The addition of carbon disulfide yielded the desired product and 1,3-dibenzylthiourea (*ca.* 1:1), whereas the alternate method involving the addition of benzylamine smoothly formed the crude product.

According to the literature,[3] chloroacetic acid, bromoacetic acid, and ethyl 2-bromoacetate could be used in the cyclization reaction of thiosemicarbazones **4a–4i** to form thiazolidin-4-ones **5a–5i**. Our experimental results showed that ethyl bromoacetate was suitable for this reaction and resulted in the best selectivity of desired products. The IR spectra of compounds **5a–5i** showed the disappearance of the strong C=S band at 1224–1271 cm^{-1} and a new band at 1715–1728 cm^{-1} attributed to the carbonyl group of thiazolidin-4-one. The ^{1}H NMR spectra showed that the signal due to C=N—N—H ($\delta > 11.14$ ppm), disappeared and a new singlet at δ 3.94–4.12 ppm attributed to the CH$_2$ of the thiazolidin-4-one ring appeared. It is noteworthy that the two protons of amino group on pyrimidine heterocycle are exhibited as two singlets, though they are shown as a broad singlet before the cyclization



SCHEME 1

reaction. The ^{13}C NMR spectra revealed new peaks at δ 31.89–32.41 ppm and δ169.13–171.65 ppm, which were due to the CH_2 and O=C carbons of thiazolidin-4-one ring respectively. In the preparation of **5f**, the assignment of ^1H NMR, ^{13}C NMR, and HRMS showed that a 1:1 stable adduct of **5f** and solvent ethanol was formed, but the ethanol could not be removed by azeotropic distillation with toluene.

EXPERIMENTAL

Melting points were measured using a CRC-1 melting point instrument and are uncorrected. The purities of thiosemicarbazones and thiazolidin-4-ones were determined by HPLC (VARIAN Prostar) equipped with a C_{18} column. FT-IR spectra were recorded on a Nicolet instrument, Avetar 370. ^{1}H NMR and ^{13}C NMR spectra were obtained on a Varian PLUS-400 spectrometer. d_6-DMSO was used as the solvent with tetramethylsilane (TMS) as the internal standard. Mass spectra (MS) were recorded on a Bruker esquire 3000 plus instrument. High resolution mass spectra (HRMS) were recorded on a Bruker Apex III (7.0 Tesla) FTICR mass spectrometer. All reagents were obtained from commercial sources and used as received. The reactions were monitored by HPLC.

4-Amino-2-methanesulfanylpyrimidine-5-carboxaldehyde (1)

It was obtained as described in the literature.[14] White powder, mp 182–184°C.

4-Methylthiosemicarbazide (3a)

To a mixture of CS_2 (45.6 g, 0.6 mol) and triethylamine (65.5 g, 0.65 mol), methylamine (38.8 g, 40%, 0.5 mol) was added dropwise with stirring at a temperature lower than 20°C. The reaction mixture was stirred for additional 3 h, and then 150 mL H_2O and hydrazine hydrate (29.4 g, 85%, 0.5 mol) was added to the mixture. The obtained mixture was refluxed for 24 h, and the hydrogen sulfide released from the reaction system and was absorbed with 30% NaOH solution. Then the reaction mixture was concentrated to about 100 mL, and the residue was cooled to 0–3°C with stirring. After filtration, ice-cold water washing, and drying with P_2O_5, the title product was obtained. Yield: 74%. White crystals, mp 134–135°C.

4-Ethylthiosemicarbazide (3b)

The procedure was the same as described for **1a**. Yield: 76%. White crystals, mp 81–83°C.

4-Propylthiosemicarbazide (3c)

To a mixture of CS_2 (45.6 g, 0.6 mol), 20 mL H_2O, and triethylamine (65.5 g, 0.65 mol), propylamine (29.5 g, 0.5 mol) was added dropwise with stirring at temperature of 15–20°C. Then the reaction procedure was similar as described for **3a**. The obtained reaction mixture was concentrated to about 100 mL, and the lower layer of the residue was separated. After being solidified, it was recrystallized from cyclohexane to give **3c**. Yield: 58%. White crystals, mp 53–54°C.

4-iso-Propylthiosemicarbazide (3d)

The reaction procedure was similar as described for **3c**. After concentration of the obtained reaction mixture to about 120 mL, the residue was cooled to room temperature. The precipitate was filtered off, cold water washed, dried, and recrystallized from ethanol to give **3d**. Yield: 63%. White crystals, mp 82–83°C.

4-Butylthiosemicarbazide (3e)

The procedure was the same as described for **3c**. Yield: 65%. White crystals, mp 65–66°C.

4-tert-Butylthiosemicarbazide (3f)

The reaction procedure was the same as described for **3d** except that a portion of product was precipitated in the course of reflux. Yield: 63%. White crystals, mp 142–143°C.

4-Cyclohexylthiosemicarbazide (3g)

The reaction procedure was the same as described for **3d**. Yield: 61%. White crystals, mp 147–148°C.

4-Benzylthiosemicarbazide (3h)

The reaction procedure was the same as described for **3d**. Yield: 76%. White crystals, mp 127–128°C.

1,6-Hexanebis(thiosemicarbazide) (3i)

To a mixture of CS_2 (45.6 g, 0.6 mol), 20 mL H_2O, and triethylamine (65.5 g, 0.65 mol), 1,6-hexanediamine (29.1 g, 0.25 mol) was added dropwise with stirring. The reaction temperature was maintained blow 20°C. Then 150 mL H_2O was added to the mixture. After stirring overnight, hydrazine hydrate (29.4 g, 85%, 0.5 mol) was added. The obtained mixture was refluxed for 24 h and then concentrated to about 120 mL. The precipitate was filtered off, cold water washed, dried, and recrystallized from ethanol to give **3i**. Yield: 64%. White crystals, mp 144–145°C.

General Procedure for the Synthesis of 4a–4i

To a solution of 4-amino-2-methanesulfanylpyrimidine-5-carboxaldehyde **1** (2 mmol) in ethanol (20 mL), N-substituted-thiosemicarbazides **3a–3h** (2 mmol) was added. After addition of several drops of acetic acid, the mixture was refluxed for 8–14 h until **1** could not be detected by HPLC. Then the reaction mixture was partially concentrated and cooled. The resulting precipitate was collected by filtration, washed with ethanol, and dried. When **4i** was the target product, 2 mmol of **1** and 1 mmol **3i** was used.

1-((4-Amino-2-(methylthio)pyrimidin-5-yl)methylene)-4-methyl thiosemicarbazide (4a)

Yield: 86%. White powder, mp > 350°C. IR $\nu_{\max}$ (KBr)/cm^{-1} 3394, 3274, 3152, 3009, 1637, 1578, 1546, 1525, 1391, 1262, 1186, 1096, 1042, 957, 784, 526. ^{1}H NMR (DMSO-d$_6$)δ 2.47 (s, 3H, S—CH$_3$), 3.00 (d, 3H, $J = 4.4$ Hz, NH—CH$_3$), 7.75 (br, s, 2H, -NH$_2$), 8.06 (s, 1H, N=CH—), 8.08 (s, 1H, pyri-H), 8.46 (s,1H, CH$_3$—NH—), 11.28 (s, 1H, C=N—NH—). ^{13}C NMR (DMSO-d$_6$)δ 13.44 (S—CH$_3$), 31.22 (NH-CH$_3$), 105.85 (pyri-C-5), 142.83 (N=CH—), 158.46 and 158.55 (pyri-C-4 and pyri-C-6), 170.68 (pyri-C-2), 176.99 (S=C—). MS (ESI) m/z 257.2 (M + H$^+$).

1-((4-Amino-2-(methylthio)pyrimidin-5-yl)methylene)-4-ethylthiosemicarbazide (4b)

Yield: 85%. White powder, mp > 350°C. IR $\nu_{\max}$ (KBr)/cm^{-1} 3404, 3315, 3143, 2997, 2930, 1637, 1572, 1531, 1363, 1241, 958, 776, 537. ^{1}H NMR (DMSO-d$_6$)δ 1.13 (t, 3H,$J = 7.2$ Hz, -CH$_3$), 2.47 (s, 3H, S-CH$_3$), 3.58 (p, 2H, $J = 6.8$ Hz, CH$_3$-CH$_2$-), 7.75 (br, s, 2H, -NH$_2$), 8.06 (s, 1H, N=CH—), 8.09 (s, 1H, pyri-H), 8.53 (s,1H, CH$_2$—NH—), 11.18 (s, 1H, C=N—NH—). ^{13}C NMR (DMSO-d$_6$)δ 13.37 (S—CH$_3$), 14.72 (-CH$_3$), 38.53 (CH$_3$—CH$_2$—), 105.85 (pyri-C-5), 142.82 (N=CH—), 158.44 and 158.56 (pyri-C-4 and pyri-C-6), 170.64 (pyri-C-2), 175.94 (S=C—). MS (ESI) m/z 271.4 (M + H$^+$).

1-((4-Amino-2-(methylthio)pyrimidin-5-yl)methylene)-4-propylthiosemicarbazide (4c)

Yield: 86%. Pale yellow crystals, mp 234–236°C. IR $\nu_{\max}$ (KBr)/cm^{-1} 3396, 3276, 3141, 2998, 2961, 2930, 2870, 1633, 1569, 1537, 1365, 1227, 1085, 961, 783. ^{1}H NMR (DMSO-d$_6$)δ 0.87 (t, 3H,$J = 7.2$ Hz, -CH$_3$), 1.53-1.63 (m, 2H, CH$_3$—CH$_2$—), 2.47 (s, 3H, S—CH$_3$), 3.49 (q, 2H, $J = 6.4$ Hz, NH—CH$_2$—), 7.76 (br, s, 2H, —NH$_2$), 8.06 (s, 1H, N=CH—), 8.09 (s, 1H, pyri-H), 8.53 (s,1H, CH$_2$—NH—), 11.19 (s, 1H, C=N—NH—). ^{13}C NMR (DMSO-d$_6$)δ 11.12 (—CH$_3$), 13.25 (S—CH$_3$), 22.11 (CH$_3$—CH$_2$—), 45.35 (NH—CH$_2$—), 105.82 (pyri-C-5), 142.65 (N=CH-), 158.35 and 158.41 (pyri-C-4 and pyri-C-6), 170.55 (pyri-C-2), 176.33 (S=C—). MS (ESI) m/z 285.3 (M + H$^+$).

1-((4-Amino-2-(methylthio)pyrimidin-5-yl)methylene)-4-isopropylthiosemicarbazide (4d)

Yield: 86%. Pale yellow crystals, mp > 350°C. IR $\nu_{\max}$ (KBr)/cm^{-1} 3387, 3277, 3129, 2962, 2930, 2869, 1634, 1572, 1516, 1464, 1370, 1300, 1241, 1154, 968, 785, 763. ^{1}H NMR (DMSO-d$_6$)δ 1.20 (d, 6H, $J = 6.4$ Hz, 2CH$_3$-), 2.46 (s, 3H, S-CH$_3$), 4.47-4.56 (m, H, NH-CH-), 7.77 (br, s, 2H, -NH$_2$), 8.06 (s, 1H, N=CH—), 8.11 (s, 1H, pyri-H), 8.13 (s,1H, CH—NH—), 11.14 (s, 1H, C=N—NH—). ^{13}C NMR (DMSO-d$_6$)δ 13.38 (S—CH$_3$), 21.85 (2CH$_3$—), 46.02 (NH—CH—), 106.01 (pyri-C-5), 142.60 (N=CH—), 158.31 and 158.54 (pyri-C-4 and pyri-C-6), 170.62 (pyri-C-2), 175.43 (S=C-). MS (ESI) m/z 285.3 (M + H$^+$).

1-((4-Amino-2-(methylthio)pyrimidin-5-yl)methylene)-4-butylthiosemicarbazide (4e)

Yield: 86%. Pale yellow crystals, mp > 350°C. IR ν_{max} (KBr)/cm^{-1} 3404, 3280, 3140, 2999, 2927, 2865, 1634, 1565, 1529, 1365, 1239, 1086, 963, 783. ^{1}H NMR (DMSO-d$_6$)δ 0.91 (t, 3H,$J = 7.2$ Hz, -CH$_3$), 1.25–1.35 (m, 2H, CH$_3$-CH$_2$-), 1.51–1.58 (m, 2H, CH$_3$—CH$_2$—CH$_2$—), 2.47 (s, 3H, S-CH$_3$), 3.53 (q, 2H, $J = 6.8$ Hz, NH-CH$_2$-), 7.79 (br, s, 2H, -NH$_2$), 8.06 (s, 1H, N=CH—), 8.09 (s, 1H, pyri-H), 8.51 (s,1H, CH$_2$—NH—), 11.19 (s, 1H, C=N—NH—). ^{13}C NMR (DMSO-d$_6$)δ 13.44 (S—CH$_3$), 13.91 (—CH$_3$), 19.71 (CH$_3$—CH$_2$—), 31.20 (CH$_3$—CH$_2$—CH—), 43.57 (NH—CH$_2$—), 105.91 (pyri-C-5), 142.77 (N=CH—), 158.49 (pyri-C-4 and pyri-C-6), 170.70 (pyri-C-2), 176.20 (S=C—). MS (ESI) m/z 299.4 (M + H$^+$).

1-((4-Amino-2-(methylthio)pyrimidin-5-yl)methylene)-4-tert-butylthiosemicarbazide (4f)

Yield: 82%. Yellow powder, mp > 350°C. IR $\nu_{\max}$ (KBr)/cm^{-1} 3372, 3279, 3128, 2971, 1633, 1571, 1524, 1371, 1264, 1191, 1075, 966, 787. ^{1}H NMR (DMSO-d$_6$)δ 1.52 (s, 9H, 3CH$_3$-), 2.46 (s, 3H, S-CH$_3$), 7.39 (s, 1H, C-NH-), 7.77 (br, s, 2H, -NH$_2$), 8.05 (s, 1H, N=CH—), 8.15 (s, 1H, pyri-H), 11.18 (s, 1H, C=N—NH—). ^{13}C NMR (DMSO-d$_6$)δ 13.79 (S—CH$_3$), 29.20

($3CH_3$—), 53.34 (NH—C—), 106.74 (pyri-C-5), 141.69 (N=CH—), 158.22 and 159.33 (pyri-C-4 and pyri-C-6), 171.00 (pyri-C-2), 175.89 (S=C—). MS (ESI) m/z 299.3 ($M + H^+$).

1-((4-Amino-2-(methylthio)pyrimidin-5-yl)methylene)-4-cyclohexylthiosemicarbazide (4g)

Yield: 85%. White powder, mp > 350°C. IR ν_{max} (KBr)/cm^{-1} 3413, 3389, 3277, 3142, 2996, 2927, 2851, 1631, 1568, 1513, 1370, 1270, 1225, 1189, 1151, 967, 784. ^1H NMR (DMSO-d_6)δ 1.10–1.16 (m, 1H, cyclohexyl-4-H_a), 1.22–1.31 (m, 2H, cyclohexyl-2-H_a, and cyclohexyl-6-H_a), 1.35–1.44 (m, 2H, cyclohexyl-3-H_a and cyclohexyl-5-H_a), 1.60–1.63 (m, 1H, cyclohexyl-4-H_b), 1.71–1.74 (m, 2H, cyclohexyl-3-H_b and cyclohexyl-5-H_b), 1.85–1.87 (m, 2H, cyclohexyl-2-H_b and cyclohexyl-6-H_b), 2.46 (s, 3H, S-CH_3), 4.16–4.18 (m, 1H, cyclohexyl-1-H), 7.78 (br, s, 2H, —NH_2), 8.06 (s, 1H, N=CH—), 8.08 (s, 1H, CH-NH-), 8.11 (s, 1H, pyri-H), 11.15 (s, 1H, C=N—NH—). ^{13}C NMR (DMSO-d_6)δ 13.41 (S—CH_3), 25.09 (cyclohexyl-C-3 and cyclohexyl-C-5), 25.27 (cyclohexyl-C-4), 31.78 (cyclohexyl-C-2 and cyclohexyl-C-6), 53.23 (cyclohexyl-C-1), 106.04 (pyri-C-5), 142.56 (N=CH—), 158.29 and 158.56 (pyri-C-4 and pyri-C-6), 170.64 (pyri-C-2), 175.41 (S=C—). MS (ESI) m/z 325.4 ($M + H^+$).

1-((4-Amino-2-(methylthio)pyrimidin-5-yl)methylene)-4-benzylthiosemicarbazide (4h)

Yield: 85%. White powder, mp > 350°C. IR ν_{max} (KBr)/cm^{-1} 3401, 3368, 3275, 3135, 2992, 2820, 1629, 1560, 1526, 1458, 1367, 1301, 1230, 1118, 1074, 967, 736. ^1H NMR (DMSO-d_6)δ 2.47 (s, 3H, S-CH_3), 4.85 (d, 2H, $J = 6.0$ Hz, NH-CH_2-), 7.21-7.35 (m, 5H, phenyl-H), 7.79 (br, s, 2H, —NH_2), 8.05 (s, 1H, N=CH—), 8.06 (s, 1H, pyri-H), 9.07 (s,1H, CH_2—NH—), 11.39 (s, 1H, C=N—NH—). ^{13}C NMR (DMSO-d_6)δ 13.33 (S-CH_3), 46.81 (NH-CH_2-), 105.75 (pyri-C-5), 126.65 (Phenyl-4-C), 126.92 (Phenyl-2-C and Phenyl-6-C), 128.17 (Phenyl-3-C and Phenyl-5-C), 139.45 (Phenyl-1-C), 143.34 (N=CH—), 158.41 and 158.69 (pyri-C-4 and pyri-C-6), 170.73 (pyri-C-2), 176.89 (S=C—). MS (ESI) m/z 333.4 ($M + H^+$).

N,N′-(Hexane-1,6-diyl)bis(2-((4-amino-2-(methylthio)pyrimidin-5-yl)methylene)hydrazinecarbothioamide) (4i)

Yield: 87%. Pale yellow powder, mp 246–249°C. IR ν_{max} (KBr)/cm^{-1} 3555, 3276, 3168, 2927, 2855, 1618, 1575, 1525, 1457, 1364, 1299, 1242, 1200, 1107, 959, 783. ^1H NMR (DMSO-d_6)δ 1.32 (s, 4H, 2NH—CH_2—CH_2—CH_2—), 1.59 (s, 4H, 2NH—CH_2—CH_2—), 2.47 (s, 6H, S-CH_3), 3.54 (q, 4H, $J = 6.4$ Hz, 2NH—CH_2—), 7.78 (br, s, 4H, 2NH_2-), 8.06 (s, 2H, 2N=CH—), 8.09 (s, 2H, 2pyri-H), 8.53 (s,2H, 2CH_2-NH-), 11.19 (s, 2H, 2C=N—NH—). ^{13}C NMR (DMSO-d_6)δ 13.38 (2S—CH_3), 26.28 (2NH—CH_2—CH_2—CH_2—), 29.03 (2NH—CH_2—CH_2—), 43.78 (2NH—CH_2—), 105.88 (2pyri-C-5), 142.78 (2N=CH—), 158.44 (2pyri-C-4 and 2pyri-C-6), 170.62 (2pyri-C-2), 176.13 (2S=C—). MS (ESI) m/z 567.3 (M + H^+).

General Procedure for the Synthesis of 5a–5i

To a mixture of thiosemicarbazones **4a–4h** (1 mmol), sodium acetate (1 mmol) in ethanol (20 mL) was added ethyl 2-bromoacetate (1.1 mol). The reaction was refluxed for 4–16 h until the thiosemicarbazones **4a–4h** were completely converted to the product. Then the reaction mixture was partially concentrated and cooled. The product was collected by filtration and was recrystallized from ethanol. When **5i** was the target product, 0.5 mmol of **4i** was needed.

2-(2-((4-Amino-2-(methylthio)pyrimidin-5-yl)methylene)hydrazono)-3-methylthiazolidin-4-one (5a)

Yield: 72%. Off-white powder, mp 275–277°C. IR ν_{max} (KBr)/cm^{-1} 3389, 3285, 2928, 1727, 1635, 1560, 1571, 1515, 1364, 1313, 1265, 1198, 1120, 786, 646, 502. ^{1}H NMR (DMSO-d_6)δ 2.51 (s, 3H, S-CH_3), 3.16 (s, 3H, -CH_3), 4.02 (s, 2H, thiazoli-CH_2-), 8.16 (br, s, 1H, —NH), 8.42 (s, 1H, N=CH—), 8.56 (s, 1H, pyri-H), 8.72 (br, s, 1H, -NH). ^{13}C NMR (DMSO-d_6)δ 13.38 (S-CH_3), 29.35 (NH—CH_3), 32.40 (thiazoli-C-5), 106.00 (pyri-C-5), 156.24 (N=CH—), 158.03 (thiazoli-C-2), 159.64 (pyri-C-4), 164.09 (pyri-C-6), 170.83 (thiazoli-C-4), 172.01 (pyri-C-2). HRMS (ESI) m/z 297.0588 (M + H^+), calcd. for $C_{10}H_{12}N_6OS_2$+ H^+ = 297.05868.

2-(2-((4-Amino-2-(methylthio)pyrimidin-5-yl)methylene)hydrazono)-3-ethylthiazolidin-4-one (5b)

Yield: 71%. Pale yellow powder, mp 223–224°C. IR ν_{max} (KBr)/cm^{-1} 3410, 3279, 2927,1723, 1620, 1566, 1518, 1451, 1368, 1338, 1262, 1195, 1128, 1049, 945, 785, 639. ^{1}H NMR (DMSO-d_6)δ 1.18 (t, 3H, $J = 6.4$ Hz, -CH_3), 2.48 (s, 3H, S-CH_3), 3.75 (q, 2H, $J = 7.2$ Hz, CH_3—CH_2—), 4.02 (s, 2H, thiazoli-CH_2-), 7.92 (br, s, 1H, —NH), 8.35 (s, 2H, N=CH— and —NH), 8.56 (s, 1H, pyri-H). ^{13}C NMR (DMSO-d_6)δ 12.26 (—CH_3), 13.38 (S—CH_3), 32.41 (thiazoli-C-5), 37.79 (N—CH_2—), 106.00 (pyri-C-5), 156.18 (N=CH—), 157.90 (thiazoli-C-2), 159.63 (pyri-C-4), 163.35 (pyri-C-6), 170.73 (thiazoli-C-4), 171.74 (pyri-C-2). HRMS (ESI) m/z 311.0740 (M + H^+), calcd. for $C_{11}H_{14}N_6OS_2$+ H^+ = 311.07433.

2-(2-((4-Amino-2-(methylthio)pyrimidin-5-yl)methylene)hydrazono)-3-propylthiazolidin-4-one (5c)

Yield: 65%. Pale yellow powder, mp 212–214°C. IR ν_{max} (KBr)/cm^{-1} 3336, 3271, 3112, 2961, 2928, 1721, 1632, 1562, 1372, 1268, 1195, 1133, 1068, 964, 786. ^{1}H NMR (DMSO-d$_6$)δ 0.88 (t, 3H, J = 7.2 Hz, -CH$_3$), 1.60–1.67 (m, 2H, CH$_3$—CH$_2$—), 2.51 (s, 3H, S—CH$_3$), 3.67 (t, 2H, J = 7.2 Hz, N—CH$_2$—), 4.04 (s, 2H, thiazoli-CH$_2$-), 8.11 (br, s, 1H, —NH), 8.41 (s, 1H, N=CH—), 8.56 (s, 1H, pyri-H), 8.64 (br, s, 1H, —NH). ^{13}C NMR (DMSO-d$_6$)δ 10.96 (—CH$_3$), 13.32 (S—CH$_3$), 19.90 (CH$_3$—CH$_2$—), 32.31 (thiazoli-C-5), 44.21 (N—CH$_2$—), 106.04 (pyri-C-5), 155.49 (thiazoli-C-2), 155.56 (N=CH—), 159.65 (pyri-C-4), 164.09 (pyri-C-6), 169.13 (thiazoli-C-4), 171.97 (pyri-C-2). HRMS (ESI) m/z 325.0897 (M + H$^+$), calcd. for $C_{12}H_{16}N_6OS_2$+ H$^+$ = 325.08998.

2-(2-((4-Amino-2-(methylthio)pyrimidin-5-yl)methylene)hydrazono)-3-isopropylthiazolidin-4-one (5d)

Yield: 65%. Pale yellow powder, mp 194–196°C. IR ν_{max} (KBr)/cm^{-1} 3353, 3277, 3134, 2965, 2927, 1721, 1630, 1603, 1560, 1382, 1358, 1270, 1195, 1122, 1068, 963, 787, 644, 575, 503. ^{1}H NMR (DMSO-d$_6$)δ 1.43 (d, 6H, J = 7.2 Hz, 2CH$_3$-), 2.48 (s, 3H, S-CH$_3$), 3.97 (s, 2H, thiazoli-CH$_2$-), 4.67-4.74 (m, 1H, N-CH-), 7.93 (br, s, 1H, —NH), 8.28 (s, 2H, N=CH— and —NH), 8.56 (s, 1H, pyri-H), ^{13}C NMR (DMSO-d$_6$)δ 13.41 (S-CH$_3$), 18.60 (2CH$_3$-), 32.21 (thiazoli-C-5), 47.28 (N—CH—), 106.00 (pyri-C-5), 156.36 (N=CH—), 159.18 (pyri-C-4), 159.61 (thiazoli-C-2), 163.25 (pyri-C-6), 171.55 (thiazoli-C-4), 171.95 (pyri-C-2). HRMS (ESI) m/z 325.0891 (M + H$^+$), calcd. for $C_{12}H_{16}N_6OS_2$+ H$^+$ = 325.08998.

2-(2-((4-Amino-2-(methylthio)pyrimidin-5-yl)methylene)hydrazono)-3-butylthiazolidin-4-one (5e)

Yield: 69%. White solid, mp 190–192°C. IR ν_{max} (KBr)/cm^{-1} 3348, 3144, 2957, 2927, 1719, 1641, 1605, 1561, 1522, 1376, 1270, 1191, 1131, 1068, 969, 785, 571. ^{1}H NMR (DMSO-d$_6$)δ 0.89 (t, 3H, J = 7.2 Hz, -CH$_3$), 1.25–1.34 (m, 2H, CH$_3$—CH$_2$—), 1.57-1.64 (m, 2H, CH$_3$—CH$_2$—CH$_2$—), 2.48 (s, 3H, S—CH$_3$), 3.71 (t, 2H, J = 7.6 Hz, NH—CH$_2$—), 4.03 (s, 2H, thiazoli-CH$_2$-), 7.92 (br, s, 1H, -NH), 8.35 (br, s, 1H, —NH), 8.36 (s, 1H, N=CH—), 8.55 (s, 1H, pyri-H), ^{13}C NMR (DMSO-d$_6$)δ 13.37 (S—CH$_3$), 13.52 (—CH$_3$), 19.40 (CH$_3$—CH$_2$—), 28.69 (CH$_3$—CH$_2$—CH$_2$—), 32.27 (thiazoli-C-5), 42.43 (N—CH$_2$—), 105.98 (pyri-C-5), 156.46 (N=CH—), 159.21 (pyri-C-4), 159.62 (thiazoli-C-2), 163.28 (pyri-C-6), 171.61 (thiazoli-C-4), 171.99 (pyri-C-2). HRMS (ESI) m/z 339.1056 (M + H$^+$), calcd. for $C_{13}H_{18}N_6OS_2$+ H$^+$ = 339.10563.

Adduct of 2-(2-((4-Amino-2-(methylthio)pyrimidin-5-yl)methylene)hydrazono)-3-tert-butylthiazolidin-4-one and ethanol (5f)

Yield: 64%. Pale yellow powder, mp 108–112°C. IR $\nu_{\max}$ (KBr)/cm^{-1} 3327, 3136, 2962, 2928, 1716, 1635, 1532, 1454, 1365, 1300, 1265, 1212, 1151, 1031, 967, 785, 602, 509. ^{1}H NMR (DMSO-d$_6$)δ 1.21 (t, 3H,J = 7.2 Hz, ethanol-CH$_3$), 1.38 (s, 9H, 3CH$_3$—), 2.46 (s, 3H, S—CH$_3$), 3.94 (s, 2H, thiazoli-CH$_2$-), 4.14 (q, 2H, J = 6.8 Hz, ethanol-CH$_2$), 5.94 (s, 1H, ethanol-OH), 8.11 (br, s, 1H, —NH), 8.17 (br, s, 1H, —NH), 8.26 (s, 1H, N=CH—), 8.31 (s, 1H, pyri-H), ^{13}C NMR (DMSO-d$_6$)δ 13.27 (S—CH$_3$), 13.95 (ethanol-CH$_3$), 28.35 (3CH$_3$—), 31.89 (thiazoli-C-5), 53.37 (N-C-), 61.29 (ethanol-CH$_2$-), 107.12 (pyri-C-5), 150.19 (N=CH—), 157.65 (thiazoli-C-2), 157.81 (pyri-C-4), 159.43 (pyri-C-6), 169.73 (pyri-C-2), 169.84 (thiazoli-C-4). HRMS (ESI) m/z 385.1476 (M + H$^+$), calcd. for $C_{15}H_{24}N_6O_2S_2 + H^+ = 385.14749$.

2-(2-((4-Amino-2-(methylthio)pyrimidin-5-yl)methylene)hydrazono)-3-cyclohexylthiazolidin-4-one (5g)

Yield: 68%. White solid, mp 241–242°C. IR $\nu_{\max}$ (KBr)/cm^{-1} 3361, 3116, 2924, 2857, 1717, 1636, 1560, 1557, 1521, 1381, 1270, 1194, 1144, 1067, 968, 787, 545. ^{1}H NMR (DMSO-d$_6$)δ 1.12–1.19 (m, 1H, cyclohexyl-4-H$_a$), 1.27-1.35 (m, 2H, cyclohexyl-2-H$_a$, and cyclohexyl-6-H$_a$), 1.62–1.64 (m, 3H, cyclohexyl-3-H$_a$, cyclohexyl-4-H$_b$ and cyclohexyl-5-H$_a$), 1.81–1.83 (m, 2H, cyclohexyl-3-H$_b$ and cyclohexyl-5-H$_b$), 2.28–2.35 (m, 2H, cyclohexyl-2-H$_b$ and cyclohexyl-6-H$_b$), 2.49 (s, 3H, S-CH$_3$), 3.98 (s, 2H, thiazoli-CH$_2$-), 4.28–4.33 (m, 1H, cyclohexyl-1-H), 7.95 (br, s, 1H, —NH), 8.38 (s, 2H, N=CH— and —NH), 8.58 (s, 1H, pyri-H). ^{13}C NMR (DMSO-d$_6$)δ 13.32 (S—CH$_3$), 24.79 (cyclohexyl-C-4), 25.53 (cyclohexyl-C-3 and cyclohexyl-C-5), 27.83 (cyclohexyl-C-2 and cyclohexyl-C-6), 32.06 (thiazoli-C-5), 55.27 (cyclohexyl-C-1), 105.97 (pyri-C-5), 156.26 (N=CH—), 158.91 (thiazoli-C-2), 159.56 (pyri-C-4), 163.40 (pyri-C-6), 171.36 (thiazoli-C-4), 171.96 (pyri-C-2). HRMS (ESI) m/z 365.1205 (M + H$^+$), calcd. for $C_{15}H_{26}N_6OS_2 + H^+ = 365.12128$.

2-(2-((4-Amino-2-(methylthio)pyrimidin-5-yl)methylene)hydrazono)-3-benzylthiazolidin-4-one (5h)

Yield: 71%. White solid, mp 227–228°C. IR $\nu_{\max}$ (KBr)/cm^{-1} 3356, 3167, 2923, 1715, 1647, 1563, 1521, 1374, 1270, 1181, 1063, 966, 783, 697, 541, 501. ^{1}H NMR (DMSO-d$_6$)δ 2.48 (s, 3H, S—CH$_3$), 4.13 (s, 2H, thiazoli-CH$_2$-), 4.91 (s, 2H, N—CH$_2$—), 7.29-7.36 (m, 5H, phenyl-H), 7.96 (br, s, 1H, -NH), 8.36 (s, 1H, N=CH—), 8.42 (br, s, 1H, —NH), 8.53 (s, 1H, pyri-H), ^{13}C NMR (DMSO-d$_6$)δ 13.83 (S—CH$_3$), 32.79 (thiazoli-C-5), 46.25 (N—CH_2—), 106.37 (pyri-C-5), 128.01 (Phenyl-C-4, Phenyl-C-2 and Phenyl-C-6), 128.96 (Phenyl-C-3 and Phenyl-C-5), 136.23 (Phenyl-C-1), 157.19 (N=CH-), 159.38 (thiazoli-C-2), 160.10 (pyri-C-4), 163.64 (pyri-C-6), 171.92 (thiazoli-C-4), 172.60 (pyri-C-2). HRMS (ESI) m/z 373.0902 (M + H^+), calcd. for $C_{16}H_{16}N_6OS_2+ H^+ = 373.08998$.

3,3′-(Hexane-1,6-diyl)bis(2-(((4-amino-2-(methylthio) pyrimidin-5-yl)methylene)hydrazono)thiazolidin-4-one) (5i)

Yield: 70%. Pale yellow powder, mp 273–276°C. IR ν_{max} (KBr)/cm^{-1} 3395, 3348, 2923, 1718, 1637, 1560, 1376, 1320, 1260, 1178, 1151, 1060, 785. ^1H NMR (DMSO-d_6)δ 1.33 (s, 4H, 2N—CH_2—CH_2—CH_2—), 1.63 (s, 4H, 2N—CH_2—CH_2—), 2.53 (s, 6H, 2S—CH_3), 3.71 (m, 4H, 2N—CH_2), 4.04 (s, 4H, 2thiazoli-CH_2-), 8.20 (s, 2H, —NH), 8.41 (s, 1H, N=CH—), 8.53 (s, 1H, pyri-H), 8.81 (s, 2H, —NH). ^{13}C NMR (DMSO-d_6)δ 13.88 (2S—CH_3), 26.04 (2NH—CH_2—CH_2—CH_2—), 26.76 (2NH—CH_2—CH_2—), 32.94 (thiazoli-C-5), 43.11 (2NH—CH_2—), 106.59 (pyri-C-5), 154.54 (thiazoli-C-2), 155.71 (N=CH—), 160.25 (pyri-C-4), 165.04 (pyri-C-6), 168.72 (thiazoli-C-4), 172.53 (pyri-C-2). HRMS (ESI) m/z 647.1554 (M + H^+), calcd. for $C_{24}H_{30}N_{12}O_2S_2+ H^+ = 647.15703$.

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