Synthesis and characterization of new pyrimidine-based 1,3,4-oxa(thia)diazoles, 1,2,4-triazoles and 4-thiazolidinones

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Abstract

New 1,2,4-triazoles **3a**,**b**, **4a**,**b**, 1,3,4-oxadiazoles **5a**,**b**, 1,3,4-thiadiazoles **6a**,**b** and 4-thiazolidinones **7a**,**b** were synthesized by cyclization of N-substituted 2-[2-(6-methyl-2-morpholinopyrimidin-4-ylthio)acetyl]hydrazinecarbothioamides **2a**,**b** under different conditions. The starting **2a**,**b** were readily obtained by acylation of 2-(6-methyl-2-morpholinopyrimidin-4-ylthio)acetohydrazide (**1**) with cyclohexyl or phenyl isothiocyanate. All new compounds were characterized by ^{1}H, ^{13}C NMR, IR spectroscopy and elemental analysis.

Keywords: Pyrimidine, 1,2,4-triazole, 1,3,4-oxadiazole, 1,3,4-thiadiazole, 4-thiazolidinone

Introduction

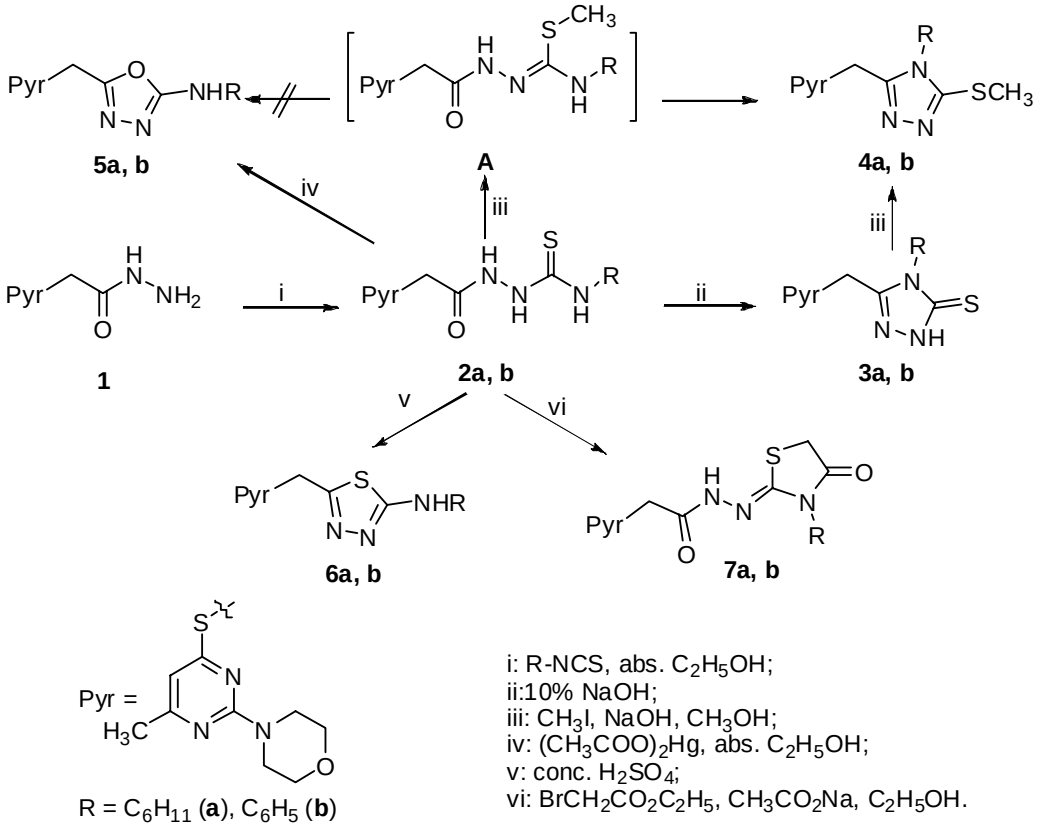
Heterocyclic structures, in particular azoles and azines, form the basis of many pharmaceutical and agrochemical products. Publications devoted to the chemistry of azoles in recent decade refer to the synthesis of 1,2,4-triazoles, 1,3,4-oxa(thia)diazoles and thiazolidines. Different approaches have been reported for the preparation of such heterocycles.[1,2] Their significance deals with a broad spectrum of biological activity and technological interest. The efficacy of clinical use of antiviral, anticancer and antifungal drugs (*Ribavirin*, *Anastrozole*, *Fluconazole*, *Voriconazole* etc.) led to intense investigation of 1,2,4-triazole derivatives. 1,2,4-Triazole containing molecules have increasing interest as anticancer,[3] fungicidal, antimicrobial,[4] antitubercular[5] or anti-inflammatory[6] agents. They also are significant in agrochemical industry as plant protecting materials.[7]

A wide range of biological activities as well as different methods of synthesis have been attributed to compounds containing 1,3,4-oxa(thia)diazole ring.[8-10] Moreover, ionic liquid-crystalline compounds bearing 1,3,4-oxadiazole moiety are of interest in emerging organic electronics OLED technologies.[11]

Thiazolidine is a biologically important scaffold and numerous pharmacological activities of 4-thiazolidinone are revealed and well documented.[12,13]

Results and Discussion

Our earlier studies involved synthesis of heterocyclic compounds containing in their structure both the pyrimidine and azole, in particular 1,2,4-triazole, rings.[14] In consideration of diverse biological properties of this type of compounds and in continuation of our interest in the synthesis of biologically active heterocycles, the aim of the present work was to develop simple and efficient procedures for the preparation of new 1,2,4-triazole, 1,3,4-oxadiazole, 1,3,4-thiadiazole and 4-thiazolidinone derivatives bearing substituted pyrimidine moiety. As a core structure for these reactions (6-methyl-2-morpholinopyrimidin-4-ylthio)acetohydrazide (**1**) was exploited.[15] Its derivatives were found to show significant anti-inflammatory activity and this was the reason of our choice to use hydrazide **1** as a starting compound. Reaction of hydrazide **1** with cyclohexyl or phenyl isothiocyanate in absolute ethanol at reflux produced the corresponding hydrazinecarbothioamides **2a**,**b** with good yields (Scheme 1).



Scheme 1

The structure of hydrazinecarbothioamides **2a**,**b** was confirmed by the spectral data. The IR spectra of componds **2a**,**b** displayed characteristic absorption bands in a region of 3235-3127 cm^{-1} for NH, at 1700-1692 cm^{-1} for C=O and in the region of 1348-1335 cm^{-1} corresponding to C=S vibrations. In the ^{1}H NMR spectra three sets of NH group proton singlets as well as signals of cyclohexyl or phenyl group protons were observed confirming **2a** and **2b** formation. The cyclization of hydrazinecarbothioamides is an excellent strategy for the synthesis of different heterocycles.[16]

The starting hydrazinecarbothioamides **2a**,**b** on treatment with 10% sodium hydroxide solution at reflux undergo cyclodehydration to give 1,2,4-triazole-3-thiones **3a**,**b**. The structure was evident from spectral data. The IR spectra displayed absorption bands at 3235-3127 cm^{-1} for NH, 1605-1595 cm^{-1} due C=N group and at 1332-1330 cm^{-1} corresponding to C=S stretch vibrations. The C=O group absorption was absent. The ^{1}H NMR spectra revealed far downfield signal of triazole NH proton at 13.89-13.60 ppm.

Hydrazinecarbothioamides **2a**,**b** were treated with iodomethane to give compound **A**. The intermediate **A** was expected to cyclize to form either 1,2,4-triazole **4** (dehydration) or 1,3,4-oxadiazole **5** (loss of CH_3SH). Reaction of **2a**,**b** with iodomethane in the presence of sodium hydroxide as a base did not proceed at room temperature, while at reflux heterocyclization to 1,2,4-triazoles **4a**,**b** took place. The same methylthio derivatives **4a**,**b** were synthesized by the direct alkylation of triazoles **3a**,**b** with iodomethane in analogous conditions. The structure assignment was made by spectral data. In the ^{1}H NMR spectra of triazoles **4a**,**b** singlets observed at 2.65 ppm (**4a**) and 2.59 ppm (**4b**) were attributed to SCH_3 protons and a signal for NH proton was absent. In the IR spectra characteristic NH group absorption was not found.

There are different methods to generate 2-amino substituted 1,3,4-oxadiazoles by oxidative cyclization of acylhydrazinecarbothioamides.[16b,17] Reactions with hydrazinecarbothioamides **2a**,**b** to give 1,3,4-oxadiazoles **5a**,**b** were carried out either using iodine/potassium iodide in sodium hydroxide solution or mercury (II) acetate in abs. ethanol. The latter method appeared to be much more convenient because of shorter reaction time, ease of work-up procedure and slightly higher yields of products **5a**,**b**.

The acid catalyzed cyclization of hydrazinecarbothioamides **2a**,**b** afforded thiadiazoles **6a**,**b**. Compounds **2a**,**b** were reacted with conc. sulfuric acid at 0 °C to give moderate yields of **6a**,**b**.

Reaction of starting **2a**,**b** with ethyl bromoacetate in abs. ethanol in the presence of anhydrous sodium acetate as a base resulted in the formation of 4-thiazolidinones **7a**,**b**. The spectral data were in accordance with given structures. Thiazolidinones **7a**,**b** show absorption bands for ring C=O in the region of 1720-1760 cm^{-1} together with amide C=O absorption at ~ 1670 cm^{-1}. The ^{1}H NMR spectra revealed the presence of two singlets for thiomethylene protons. Another pair of singlets equivalent to two protons at 4.02, 4.05 (for **7a**) and 4.10, 4.07 ppm (for **7b**) correspond to C-5 protons of the 4-thiazolidinone ring. Peaks resonated at 28.3 and 30.6 ppm in the ^{13}C NMR were assigned to thiazolidinone C-5, while at 158.5 and 148.2 ppm were attributed to C-2 of the 4-thiazolidinone ring.

In conclusion, a simple and effective procedure for the preparation of novel 1,2,4-triazoles, 1,3,4-oxadiazoles, 1,3,4-thiadiazoles and 4-thiazolidinones from a common (6-methyl-2-morpholinopyrimidin-4-ylthio)acetohydrazide intermediate was developed.

Experimental Section

General. Melting points were determined in open capillaries and are uncorrected. The IR spectra were recorded on a Spectrum BX FT-IR (Perkin-Elmer, Sweden) as potassium bromide pellets. The NMR spectra were recorded on a Unity Varian Inova spectrometer at 300 MHz for ^{1}H and 75 MHz for ^{13}C, chemical shifts (δ) are reported in ppm relative to TMS. The course of reactions and purity of compounds was controlled by TLC on Alugram Sil G/UV$_{254}$ plates (ethyl acetate/hexane = 3/1). Elemental analyses were performed at the Microanalytical Laboratory of the Department of Organic Chemistry of Vilnius University. Chemicals were purchased from Sigma-Aldrich. All solvents were dried and distilled before use.
(6-Methyl-2-morpholinopyrimidin-4-ylthio)acetohydrazide (**1**) was synthesized as earlier reported.[15]

General procedure for the synthesis of 2a,**b**
A mixture of hydrazide **1** (2.83 g, 10 mmol) and cyclohexyl (or phenyl) isothiocyanate (11 mmol) in abs. ethanol (50 ml) was refluxed for 3 h and then cooled to room temperature. The resultant white solid was collected by filtration, dried and crystallized from ethanol.
***N*-Cyclohexyl-2-[2-(6-methyl-2-morpholinopyrimidin-4-ylthio)acetyl]hydrazinecarbothioamide (2a).** Yield 73%, mp 204-206 °C; ^{1}H NMR (DMSO-*d*$_6$), δ, ppm: 1.12-1.23, 1.65-1.79 (2m, 10H, cyclohexyl), 2.21 (s, 3H, CH_3), 3.66-3.71 (m, 8H, morpholine), 3.92 (s, 2H, SCH_2), 4.03-4.06 (m, 1H, cyclohexyl), 6.55 (s, 1H, C*H*-pyrimidine), 7.29 (s br, 1H, N*H*-cyclohexyl), 9.26 (s, 1H, N*H*CS), 10.0 (s, 1H, CON*H*); ^{13}C NMR (DMSO-*d*$_6$), δ, ppm: 24.3, 25.5, 25.9, 31.6, 32.6, 44.5, 53.3, 66.7, 106.9, 161.1, 166.4, 167.9, 168.4, 181.0; IR, ν, cm^{-1}: 3235, 3138 (NH), 2931, 2854 (CH), 1700 (C=O), 1550, 1497 (C=C, C=N), 1445 (CH_3), 1335 (C=S), 1293 (S-CH_2), 1117 (C-O-C). Anal. Calcd. for $C_{18}H_{28}N_6O_2S_2$: C, 50.92; H, 6.65; N, 19.79. Found: C, 50.81; H, 6.53; N, 19.65.
2-[2-(6-Methyl-2-morpholinopyrimidin-4-ylthio)acetyl]-*N*-phenylhydrazinecarbothioamide (2b). Yield 84%, mp 191-193 °C; ^{1}H NMR (DMSO-*d*$_6$), δ, ppm: 2.22 (s, 3H, CH_3), 3.62-3.68 (m, 8H, morpholine), 3.98 (s, 2H, SCH_2), 6.57 (s, 1H, CH-pyrimidine), 7.18-7.30 (m, 1H, phenyl), 7.32-7.37 (m, 4H, phenyl), 9.50 (s br, 1H, N*H*-Ph), 9.75 (s, 1H, N*H*CS), 10.29 (s, 1H, CON*H*); ^{13}C NMR (DMSO-*d*$_6$), δ, ppm: 24.3, 31.7, 44.5, 66.7, 107.0, 125.9, 126.4, 128.9, 139.7, 161.1, 166.4, 168.0, 168.4, 181.5; IR, ν, cm^{-1}: 3200, 3127 (NH), 2952, 2854 (CH), 1692 (CO), 1598, 1548, 1495 (C=C, C=N), 1442 (CH_3), 1348 (C=S), 1293 (S-CH_2),1118 (C-O-C). Anal. Calcd. for $C_{18}H_{22}N_6O_2S_2$: C, 51.65; H, 5.30; N, 20.08. Found: C, 51.81; H, 5.39; N, 19.84.

General procedure for the synthesis of 3a,**b**

A mixture of compound **2a** or **2b** (1 mmol) and 10% sodium hydroxide solution (20 ml) was heated at reflux for 3 h, cooled to room temperature, poured over crushed ice and acidified with conc. HCl to pH 5. The precipitate was collected by filtration, washed with water, dried and crystallized from ethanol.

4-Cyclohexyl-5-[(6-methyl-2-morpholinopyrimidin-4-ylthio)methyl]-2*H*-1,2,4-triazole-3(4*H*)-thione (3a). Yield 79%, mp 213-215 °C; ^{1}H NMR (DMSO-d_6), δ, ppm: 1.15-1.18, 1.69-1.79 (2m, 10H, cyclohexyl), 2.24 (s, 3H, CH_3), 3.64-3.66, 3.72-3.75 (2m, 8H, morpholine), 4.29 (s br, 1H, cyclohexyl) 4.67 (s, 2H, SCH_2), 6.61 (s, 1H, CH-pyrimidine), 13.60 (s, 1H, NH); ^{13}C NMR (DMSO-d_6), δ, ppm: 23.3, 24.3, 25.2, 26.1, 29.1, 44.6, 57.0, 66.7, 107.3, 149.8, 160.8, 166.8, 166.9, 167.1; IR, ν, cm^{-1}: 3236 (NH), 2936, 2853 (CH), 1554, 1508, 1467 (C=C, C=N), 1435 (CH_3), 1330 (C=S), 1292 (S-CH_2), 1109 (C-O-C). Anal. Calcd. for $C_{18}H_{26}N_6OS_2$: C, 53.17; H, 6.45; N, 20.67. Found: C, 53.35; H, 6.39; N, 20.41.

5-[(6-Methyl-2-morpholinopyrimidin-4-ylthio)methyl]-4-phenyl-2*H*-1,2,4-triazole-3(4*H*)-thione (3b). Yield 85%, mp 198-200°C; ^{1}H NMR (DMSO-d_6), δ, ppm: 2.18 (s, 3H, CH_3), 3.59-3.62 (m, 8H, morpholine), 4.38 (s, 2H, SCH_2), 6.44 (s, 1H, CH-pyrimidine), 7.41-7.44, 7.51-7.53 (2m, 5H, phenyl), 13.89 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6), δ, ppm: 21.4, 23.6, 44.5, 66.6, 107.4, 127.9, 130.6, 131.1, 132.7, 153.0, 158.9, 161.5, 171.2, 171.6; IR, ν, cm^{-1}: 3242 (NH), 2986, 2850 (CH), 1606, 1558, 1507 (C=C, C=N), 1442 (CH_3), 1289 (S-CH_2), 1111 (C-O-C). Anal. Calcd. for $C_{18}H_{20}N_6OS_2$: C, 53.98; H, 5.03; N, 20.98. Found: C, 54.14; H, 4.96; N, 21.13.

4-Cyclohexyl-5-methylthio-3-[(6-methyl-2-morpholinopyrimidin-4-ylthio)methyl]-1,2,4-triazole (4a). Method A. A solution of iodomethane (0.185 g, 1.3 mmol) and methanol (5 ml) was added dropwise to a mixture of triazole **3a** (0.41 g, 1 mmol), sodium hydroxide (0.04 g, 1 mmol) and methanol (10 ml) under stirring. The reaction mixture was heated at reflux for 2 h and distilled under reduced pressure. The residue was dissolved in water, neutralized with diluted HCl and extracted with chloroform. The extracts were dried under Na_2SO_4 and evaporated to give a white solid of **4a**. Yield 0.29 g (69%), mp 178-180 °C (from 2-propanol); ^{1}H NMR (DMSO-d_6), δ, ppm: 1.30-1.36, 1.60-1.62, 1.78-1.81, 1.99-2.03 (4m, 10H, cyclohexyl), 2.24 (s, 3H, CH_3), 2.65 (s, 3H, SCH_3), 3.64-3.66, 3.67-3.76 (2m, 8H, morpholine), 4.05-4.13 (m, 1H, cyclohexyl) 4.75 (s, 2H, SCH_2), 6.63 (s, 1H, CH-pyrimidine); ^{13}C NMR (DMSO-d_6), δ, ppm: 15.9, 22.8, 24.1, 25.2, 25.8, 30.8, 44.7, 56.4, 66.7, 107.2, 151.2, 153.2, 160.3, 166.5, 167.6. IR, ν, cm^{-1}: 2932, 2854 (CH), 1605, 1549, 1498 (C=C, C=N), 1445 (CH_3), 1293 (S-CH_2), 1121 (C-O-C). Anal. Calcd. for $C_{19}H_{28}N_6OS_2$: C, 54.26; H, 6.71; N, 19.98. Found: C, 54.01; H, 6.89; N, 20.11.

Method B. A solution of sodium hydroxide (0.04 g, 1 mmol) in methanol (5 ml) was added dropwise at room temperature to a stirred mixture of hydrazinecarbothioamide **2a** (0.42 g, 1 mmol) and iodomethane (0.185 g, 1.3 mmol) in methanol (10 ml). The reaction mixture was then heated at reflux for 1 h and the solvent was removed under reduced pressure. The residue was dissolved in water, neutralized with diluted HCl and extracted with chloroform. The extracts

were dried under Na_2SO_4 and evaporated to give **4a**, 0.28 g (67%), mp 178-180 °C (from 2-propanol).

3-[(6-Methyl-2-morpholinopyrimidin-4-ylthio)methyl]-5-methylthio-4-phenyl-1,2,4-triazole (4b) was synthesized as **4a**. **Method A.** Yield 88 %, mp 189-190°C (from ethanol-water 5/1). **Method B.** yield 81%, mp 190-192°C; ^{1}H NMR (DMSO-d_6), δ, ppm: 2.18 (s, 3H, CH_3), 3.61 (m, 8H, morpholine), 4.51 (s, 2H, SCH_2), 6.43 (s, 1H, CH-pyrimidine), 7.43-7.46, 7.53-7.55 (2m, 5H, phenyl); ^{13}C NMR (DMSO-d_6), δ, ppm: 15.0, 22.3, 24.2, 66.7, 107.0, 127.9, 130.5, 130.7, 133.2, 152.7, 153.2, 160.6, 166.6, 166.9. IR, ν, cm^{-1}: 2957, 2847 (CH), 1596, 1550, 1499 (C=C, C=N), 1440 (CH_3), 1293 (S-CH_2), 1120 (C-O-C). Anal. Calcd. for $C_{19}H_{22}N_6OS_2$: C, 55.05; H, 5.35; N, 20.27. Found: C, 54.95; H, 5.18; N, 20.39.

2-Cyclohexylamino-5-[(6-methyl-2-morpholinopyrimidin-4-ylthio)methyl]-1,3,4-oxadiazole (5a). Method A. Iodine in a 5% solution of potassium iodide in ethanol was added dropwise to a cooled (5-7 °C) mixture of hydrazinecarbothioamide **2a** (0.42 g, 1 mmol), ethanol (7 ml) and 2 N sodium hydroxide solution (0.7 ml) under stirring till the color of iodine persisted. The reaction mixture was allowed to warm to room temperature and then was heated at 45-50°C for 2 hours. The solvent was removed in vacuum, the residue was poured over crushed ice and neutralized with acetic acid. The solid formed was filtered of, washed with water, dried and crystallized from benzene to give 0.22 g (57%) of **5a**, mp 159-160 °C; ^{1}H NMR (DMSO-d_6), δ, ppm: 1.14-1.29, 1.51-1.58, 1.63-1.73, 1.82-1.91 (4m, 10H, cyclohexyl), 2.21 (s, 3H, CH_3), 3.20-3.29 (m, 1H, cyclohexyl), 3.61-3.64, 3.69-3.72 (2m, 8H, morpholine), 4.47 (s, 2H, SCH_2), 6.57 (s, 1H, CH-pyrimidine), 7.51 (d, J = 9 Hz, 1H, NH); ^{13}C NMR (DMSO-d_6), δ, ppm: 22.7, 24.3, 25.1, 32.9, 44.5, 52.4, 66.7, 107.0, 157.0, 160.9, 163.6, 166.8, 167.1; IR, ν, cm^{-1}: 3332, 3250 (NH), 2931, 2853 (CH), 1578, 1552, 1509 (C=C, C=N), 1447 (CH_3), 1294 (S-CH_2), 1225, 1023 (C-O-C oxadiazole), 1119 (C-O-C). Anal. Calcd. for $C_{18}H_{26}N_6O_2S$: C, 55.36; H, 6.71; N, 21.52. Found: C, 55.32; H, 6.80; N, 21.67.

Method B. A mixture of hydrazinecarbothioamide **2a** (0.42 g, 1 mmol) and mercury (II) acetate (0.32 g, 1 mmol) in ethanol (15 ml) was heated at reflux for 30 min. and filtered off. The solvent was evaporated in vacuum, the solid was crystallized from benzene to give 0.34 g (87%) of **5a**, mp 159-160 °C.

5-[(6-Methyl-2-morpholinopyrimidin-4-ylthio)methyl]-2-phenylamino-1,3,4-oxadiazole (5b). This was synthesized in a similar manner to **5a** using **Method B.** Yield 89%, mp 178-180 °C (from tetrahydrofuran); ^{1}H NMR (DMSO-d_6), δ, ppm: 2.22 (s, 3H, CH_3), 3.60-3.62, 3.70-3.72 (m, 8H, morpholine), 4.60 (s, 2H, SCH_2), 6.60 (s, 1H, CH-pyrimidine), 7.00 (t J = 8 Hz, 1H, phenyl), 7.33 (t J = 8 Hz, 2H, phenyl), 7.52 (d J = 8 Hz, 2H, phenyl), 10.47 (s, 1H, NH); ^{13}C NMR (DMSO-d_6), δ, ppm: 22.6, 24.3, 44.5, 66.7, 107.0, 117.6, 122.5, 129.8, 139.3, 157.9, 160.6, 160.9, 166.9, 167.0; IR, ν, cm^{-1}: 3260 (NH), 2918, 2852 (CH), 1603, 1552, 1500 (C=C, C=N), 1449 (CH_3), 1294 (S-CH_2), 1225, 1015 (C-O-C oxadiazole), 1119 (C-O-C). Anal. Calcd. for $C_{18}H_{20}N_6O_2S$: C, 56.23; H, 5.24; N, 21.86. Found: C, 56.35; H, 5.28; N, 21.75.

2-Cyclohexylamino-5-[(6-methyl-2-morpholinopyrimidin-4-ylthio)methyl]-1,3,4-thiadiazole (6a). Hydrazinecarbothioamide **2a** (0.42 g, 1 mmol) was added in portion to conc. sulfuric acid

(7 ml) at 0-5 °C and stirred for 0.5 h at this temperature. The reaction mixture was then allowed to warm to room temperature, poured over crushed ice-water and neutralized with 25% ammonia. The white solid was collected by filtration, washed with water, dried and crystallized to give 0.23 g (56%) of **3a**, mp 169-171 °C (from ethanol); ^{1}H NMR (DMSO-d_6), δ, ppm: 1.21-1.24, 1.54-1.58, 1.63-1.66, 1.90-1.94 (4m, 11H, cyclohexyl), 2.21 (s, 3H, CH_3), 3.63-3.76 (m, 8H, morpholine), 4.56 (s, 2H, SCH_2), 6.55 (s, 1H, CH-pyrimidine), 7.57 (d, J = 6 Hz, 1H, NH); ^{13}C NMR (DMSO-d_6), δ, ppm: 24.3, 25.0, 25.9, 27.6, 32.8, 44.7, 54.0, 66.8, 107.2, 155.6, 160.8, 166.8, 167.3, 169.0; IR, ν, cm^{-1}:3228 (NH), 2924, 2850 (CH), 1557, 1487 (C=C, C=N), 1450 (CH_3), 1294 (S-CH_2), 1088 (C-O-C). Anal. Calcd. for $C_{18}H_{26}N_6OS_2$: C, 53.17; H, 6.45; N, 20.67. Found: C, 53.31; H, 6.39; N, 20.61.

5-[(6-Methyl-2-morpholinopyrimidin-4-ylthio)methyl]-2-phenylamino-1,3,4-thiadiazole (6b). This compound was synthesized in a manner analogous to **3a** from hydrazinecarbothioamide **2a** (0.42 g, 1 mmol). Yield 0.23 g (57 %), mp 178-180 °C (ethanol); ^{1}H NMR (DMSO-d_6), δ, ppm: 2.24 (s, 3H, CH_3), 3.65-3.78 (m, 8H, morpholine), 4.69 (s, 2H, SCH_2), 6.61 (s, 1H, CH-pyrimidine), 7.00-7.03 (t, J = 7.8 Hz, 1H, phenyl), 7.32-7.37 (t, J = 7.8 Hz, 2H, phenyl), 7.57-7.60 (d, J = 7.8 Hz, 2H, phenyl), 10.26 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6), δ, ppm: 22.6, 28.0, 45.2, 66.6, 107.4, 118.2, 122.7, 129.8, 141.2, 157.7, 163.3, 165.879, 170.6; IR, ν, cm^{-1}: 3256 (NH), 2976, 2850 (CH), 1606, 1553, 1504 (C=C, C=N), 1445 (CH_3), 1282 (S-CH_2), 1118 (C-O-C). Anal. Calcd. for $C_{18}H_{20}N_6OS_2$: C, 53.98; H, 5.03; N, 20.98. Found: C, 53.69; H, 4.90; N, 21.12.

***N′*-(Cyclohexyl-4-oxo-1,3-thiazolidin-2-ylidene)-2-(6-methyl-2-morpholinopyrimidin-4-ylthio)acetohydrazide (7a).** A mixture of **2a** (0.42 g, 1 mmol), sodium acetate (0.33 g, 4 mmol) and ethyl bromoacetate (0.18 g, 1.2 mmol) in abs. ethanol (15 ml) was refluxed for 3 h. Then the solvent was removed in vacuum, the residue was triturated with water and extracted with chloroform. After evaporation of dried organic extracts, the white solid was crystallized from 2-propanol to give **7a**. Yield 0.38 g (83%), mp 180-182 °C; ^{1}H NMR (DMSO-d_6), δ, ppm: 1.20-1.33, 1.53-1.64, 1.77-1.80 (3m, 8H, cyclohexyl), 2.21 (s, 3H, CH_3), 2.27-2.31 (m, 2H, cyclohexyl), 3.63-3.65, 3.69-3.71 (2m, 8H, morpholine), 3.92, 4.11 (2s, 2H, SCH_2), 4.02, 4.05 (2s, 2H, thiazolidine), 4.19-4.27 (m, 1H, cyclohexyl), 6.56 (s, 1H, CH-pyrimidine), 10.37 (s, 1H, NH); ^{13}C NMR (DMSO-d_6), δ, ppm: 24.3, 25.5, 26.2, 28.3, 32.0, 33.1, 44.6, 55.7, 66.8, 106.9, 158.5, 161.0, 164.8, 166.2, 168.7, 172.2; IR, ν, cm^{-1}: 3272 (NH), 2927, 2854 (CH), 1720, 1670 (C=O), 1598, 1552, 1510 (C=C, C=N), 1451 (CH_3), 1294 (S-CH_2), 1116 (C-O-C). Anal. Calcd. for $C_{20}H_{28}N_6O_3S_2$: C, 51.70; H, 6.07; N, 18.09. Found: C, 51.51; H, 6.09; N, 17.99.

2-(6-Methyl-2-morpholinopyrimidin-4-ylthio)-*N′*-(4-oxo-3-phenyl-1,3-thiazolidin-2-ylidene)-acetohydrazide (7b) was synthesized in a manner analogous to **7a**. Yield 69%, mp 206-208 °C (ethanol); ^{1}H NMR (DMSO-d_6), δ, ppm: 2.18 (s, 3H, CH_3), 3.57-3.59, 3.66-3.68 (2m, 8H, morpholine), 4.15, 4.02 (2s, 2H, SCH_2), 4.10, 4.07 (2s, 2H, thiazolidine), 6.55 (s, 1H, pyrimidine), 6.86 (d, J = 8 Hz, 2H, phenyl), 7.15 (t, J = 8 Hz, 1H, phenyl), 7.38 (t, J = 8 Hz, 2H, phenyl), 11.00 (s, 1H, NH); ^{13}C NMR (DMSO-d_6), δ, ppm: 24.3, 30.6, 31.1, 44.5, 66.7, 106.8, 121.3, 125.2, 130.1, 136.3, 148.2, 161.0, 166.4, 167.0, 168.0, 169.0; IR, ν, cm^{-1}: 3229 (NH),

2917, 2846 (CH), 1760, 1669 (C=O), 1593, 1553, 1506 (C=C, C=N), 1445 (CH_3), 1295 (S-CH_2), 1119 (C-O-C). Anal. Calcd. for $C_{20}H_{22}N_6O_3S_2$: C, 52.38; H, 4.84; N, 18.33. Found: C, 52.50; H, 5.01; N, 18.32.

References

1. For recent reviews: (a) Cella, R.; Stefani, H. A. *Tetrahedron* **2009**, *65*, 2619. (b) Ali, A. A.; Brown, A. B.; El-Emary, T. I.; Ewas, A. M. M.; Ramadan, M. *Arkivoc* **2009**, (*i*), 150. (c) Martins, M. A. P.; Frizzo, C. P.; Moreira, D. N.; Zanatta, N.; Bonacorso, H. G. *Chem. Rew.* **2008**, *108*, 2015. (d) Al-Masoudi I. A.; Al-Soud Y. A.; Al-Salihi N. J.; Al-Masoudi N. A. *Chem. Heterocycl. Comp.* **2006**, *42*, 1377.
2. For some recent examples: (a) Saiz, C.; Pizzo, Ch.; Manta, E.; Wipf, P.; Mahler, S. G. *Tetrahedron Lett*. **2009**, *50*, 901. (b) Dobrota, C.; Paraschivescu, C. C.; Dumitru, I.; Matache, M.; Baciu, I.; Ruta, L.L. *Tetrahedron Lett*. **2009**, *50*, 1889. (c) Surya K. De; Stebbins, J. L.; Riel-Mehan, M.; Machleidt, T.; Dahl, R.; Yuan, H.; Emdadi, A.; Barile, E.; Chen, V.; Murphy, R.; Pellecchia, M. *J. Med. Chem*. **2009**, *52*, 1943. (d) Garfunkle, J.; Ezzili, C.; Rayl, T. J.; Hochstatter, D. G.; Hwang, I.; Boger, D. L. *J. Med. Chem.* **2008**, *51*, 4392.
3. (a) Mavrova, A. Ts.; Wesselinova, D.; Tsenov, Y. A.; Denkova, P. *Eur. J. Med. Chem*. **2009**, *44*, 63. (b) Zhang, Q.; Peng, Y.; Wang, X. I.; Keenan S. M.; Arora, S.; Welsh, W. J. *J. Med. Chem*. **2007**, *50*, 749.
4. (a) Bayrak, H.; Demirbas, A.; Karaoglu, S. A.; Demirbas, N. *Eur. J. Med. Chem*. **2009**, *44*, 1057. (b) Ezabadi, I. R.; Camoutsis, C.; Zoumpoulakis, P.; Geronikaki, A.; Sokovic, M.; Glamocilija, J.; Ciric, A. *Bioorg. Med. Chem*. **2008**, *16*, 1150. (c) Wei, Q.-L.; Zhang, S.-S.; Jun Gao, Li, W.; Xu, L.-Z.; Yu, Z.-G. *Bioorg. Med. Chem*. **2006**, *14*, 7146.
5. (a) Joshi, S. D.; Vagdevi, H. M.; Vaidya, V. P.; Gadaginamath, G. S. *Eur. J. Med. Chem*. **2008**, *43*, 1989. (b) Shiradkar, M. R.; Murahari, K. K.; Gangadasu, H. R.; Suresh, T.; Kalyan, C. A. et al. *Bioorg. Med. Chem*. **2007**, *15*, 3997.
6. (a) Kumar, H.; Javed, S. A.; Khan, S. A.; Amir, M. *Eur. J. Med. Chem*. **2008**, *43*, 2688. (b) Tozkoparan, B.; Kupeli, E.; Yesilada, E.; Ertan, M. *Bioorg. Med. Chem*. **2007**, *15*, 1808. (c) Salgin-Goksen, U.; Gokhan-Kelekci, N.; Goktas, O.; Koysal, Y.; Kilic, E.; Isik, S.; Aktay, G.; Ozalp, M. *Bioorg. Med. Chem*. **2007**, *15*, 5738.
7. (a) Cudworht, D. P.; Hegde, V. B.; Yap, M. C. H.; Guenthenspberger, K. A.; Hamilton, Ch. T.; Pechacek, J. T. et al. *J. Agric. Food Chem*. **2007**, *55*, 7517. (b) Ma, Y.; Liu, R.; Gong, X.; Li, Z.; Huang, Q.; Wang, H.; Song, G. *J. Agric. Food Chem*. **2006**, *54*, 7724.
8. Kudelko, A.; Zielinski, W. *Tetrahedron* **2009**, *65*, 1200.
9. Katritzky, A. R.; Mohapatra, P. P. ; Huang, L. *Arkivoc* **2008**, (*ix*), 62.
10. (a) Karthikeyan, M. S.; Prasad, D. J.; Mahalinga, M.; Holla, B. S.; Kumari, N. S. *Eur. J. Med. Chem*. **2008**, *43*, 25. (b) Bhandari, S. V.; Bothara, K. G.; Raut, M. K.; Patil, A. A.; Sarkate, A. P.; Mokale, V. J. *Bioorg. Med. Chem*. **2008**, *16*, 1822.

11. (a) Ho, Y. W.; Yao, W. H. *Dyes Pigments* **2009**, *82*, 6. (b) Wolarz, E.; Chrzumnicka, E.; Fischer, T.; Stumpe, J. *Dyes Pigments* **2007**, *75*, 753. (c) Zhang, X.; Tang, B.; Zhang, P.; Li, M.; Tian, W. *J. Mol. Struct.* **2007**, *846*, 55. (d) Inoue, H.; Egawa, M.; Seo, S. U.S. Patent 2007085072; *Chem. Abstr*. **2007**, *146*, 402092.
12. (a) Verma, A.; Saraf, S. K. *Eur. J. Med. Chem*. **2008**, *43*, 897. (b) Zhou, H.; Wu, S.; Zhai, S.; Liu, A.; Sun, Y.; Li, R.; Zhang, Y.; Ekins, S.; Swaan, P. W.; Fang, B.; Zhang, B.; Yan, B. *J. Med. Chem*. **2008**, *51*, 1242. (c) Geronikaki, A.; Eleftheriou, P.; Vicini, P.; Alman, I.; Dixit, A.; Saxena, A. K. *J. Med. Chem*. **2008**, *51*, 5251.
13. (a) Kucukguzel, G.; Kocatepe, A.; Clercq, E.; Sahin, F.; Gulluce, M. *Eur. J. Med. Chem*. **2006**, *41*, 353. (b) Ravichandran, V.; Prashantha Kumar, B. P.; Sankar, S.; Agrawal, R. K. *Eur. J. Med. Chem*. **2009**, *44*, 1180.
14. (a) Burbuliene, M. M.; Jakubkiene, V.; Mekuskiene, G.; Vainilavicius, P. *Phosphorus, Sulfur, and Silicon* **2003**, *178*, 2431. (b) Smičius, R.; Burbulienė, M. M.; Jakubkienė, Udrėnaitė, E.; Vainilavičius, P. *J. Heterocyclic Chem*. **2007**, *44*, 279.
15. Burbuliene, M. M.; Jakubkiene, V.; Mekuskiene, G.; Udrenaite, E.; Smicius, R.; Vainilavicius, P. *Il Farmaco* **2004**, *59*, 767.
16. For representative examples: (a) Deprez-Poulain, R. F.; Charton, J.; Leroux, V.; Deprez, B. P. *Tetrahedron Lett*. **2007**, *48*, 8157 and references therein. (b) Rivera, N. R.; Balsells, J.; Hansen, K. B. *Tetrahedron Lett*. **2006**, *47*, 4889. (c) Suni, M. M.; Nair, V. A.; Joshua, C. P. *Tetrahedron* **2001**, *57*, 2003.
17. (a) El-Essawy, F. A.; Khattab, A. F.; Abdel-Rahman, A. A.-H. *Monatsh. Chem*. **2007**, *138*, 777. (b) Amir, M.; Kumar, S. *Acta Pharm*. **2007**, *57*, 31. (c) Amir, M.; Kumar, H.; Javed, S. A. *Arch. Pharm. Chem. Life Sci*. **2007**, *340*, 577.