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Synthesis of 5-(bis((5-phenyl-1,3,4-oxadiazol-2-yl)methylthio) methylene)-2-(4-substituted benzylthio)-pyrimidine-4,6-(1*H*,5*H*)-dione derivatives

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A new series of 5-(bis((5-phenyl-1,3,4-oxadiazol-2-yl)methylthio)-methylene)-2-(4-substitutedbenzylthio)-pyrimidine-4,6-(1*H*,5*H*)-dione derivatives **(3 a–j)** was synthesized. The newly synthesized compounds were characterized by ^{1}H NMR, ^{13}C NMR, mass, IR and elemental analysis.

Key words: bis-oxadiazolthiopyrimidine-diones, thiobarbituric acid, carbon disulfide, 1,3,4-oxadiazole

INTRODUCTION

Heterocycles, the largest classical division of organic chemistry, are of immense importance biologically, industrially and indeed to the functioning of any developed human society. Over the years, five- and six-membered heterocycles, viz. barbituric acid, thiobarbituric acid, oxadiazole and thiadiazole derivatives, have emerged as an interesting class of compounds with a wide range of applications in pharmaceutical chemistry. In the past decade, dihydropyrimidines (DHPMS) and their derivatives have attracted considerable interest because of their promising activity as calcium channel blockers, antihypertensive agents, α-1a-antagonists and neuropeptide Y (NPY) antagonists [1]. Fused pyrimidines are used in a variety of agrochemicals, natural and veterinary products [2–4]. Pyrimidine derivatives and heterocyclic annulated pyrimidines exhibit a wide variety of interesting biological effects such as antiproliferative [5], antiviral [6], antitumour [7], anti-inflammatory [8], antitubercular [9], antihistaminic [10] and analgesic activities [11].

1,3,4-Oxadiazoles display a broad spectrum of biological activities such as antiHIV, antibacterial and antifungal [12, 13]. 1,3,4-Thiadiazoles are associated with diverse biological properties, probably due to the toxophoric –N–C–S group [14]. In fact, the advent of sulfur drugs and the discovery of mesoionic compounds have greatly accelerated the rate of progress in the field of thiadiazoles. 5-Unsubstituted 1,3,4-thiadiazoles are used as intermediates in the synthesis of the therapeutically potent antibiotic cefazolin [15]. Indeed, we have developed a new class of bis-heterocycles having two different heterocyclic rings, and studied their biological activities [16]. However, to our knowledge, there are no reports about the synthesis of tris-heterocyclic systems. The present communication deals with the synthesis of hitherto unknown tris heterocycles.

RESULTS AND DISCUSSION

Chemistry

The synthesis of 5-(bis((5-phenyl-1,3,4-oxadiazol-2-yl)methylthio)methylene)-2-(4-substituted benzylthio)-pyrimidine-4,6-(1*H*, 5*H*)-dione derivatives **(3 a–j)** was achieved through the versatile and efficient synthetic route outlined in Scheme. The desired compounds were synthesized as follows. Initially [17], when thiobarbituric acid **(1)** had been treated with carbon disulfide, 1,3,4-oxadiazole in the presence of

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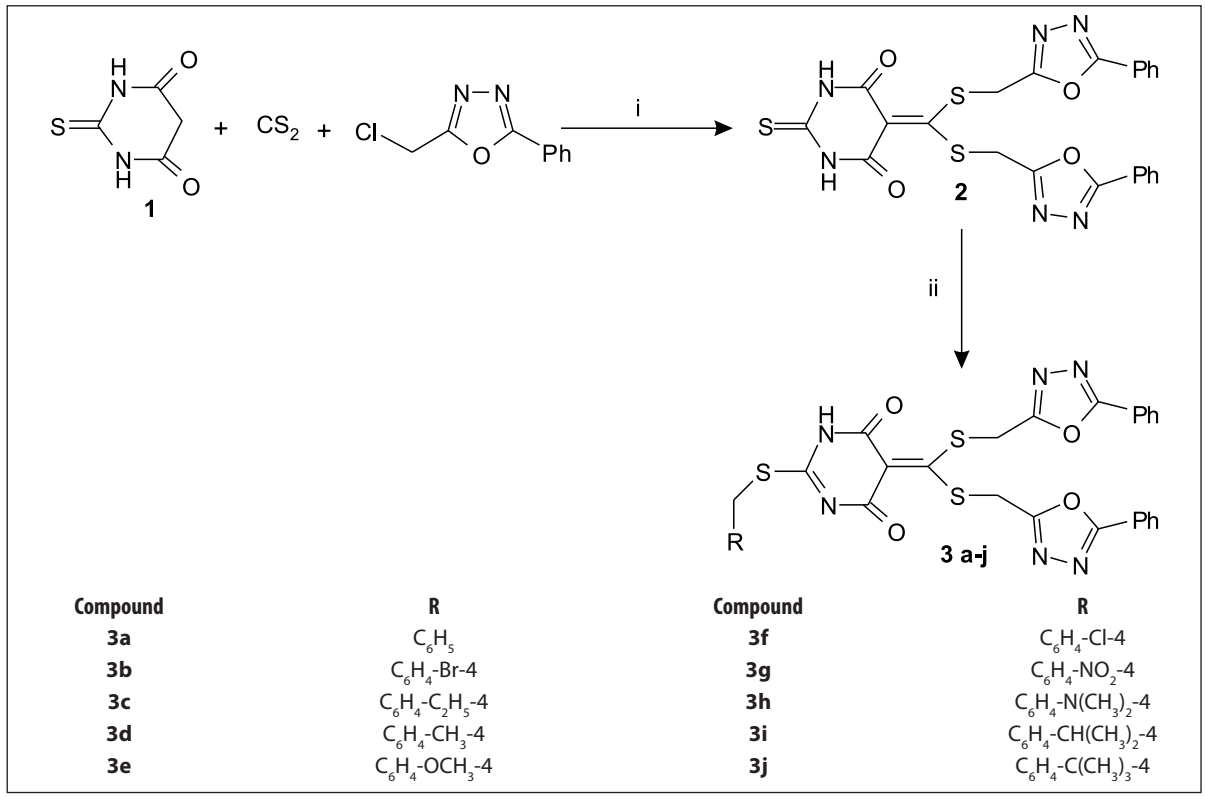

Compound	R	Compound	R
3a	C_6H_5	**3f**	C_6H_4-Cl-4
3b	C_6H_4-Br-4	**3g**	C_6H_4-NO_2-4
3c	C_6H_4-C_2H_5-4	**3h**	C_6H_4-$N(CH_3)_2$-4
3d	C_6H_4-CH_3-4	**3i**	C_6H_4-$CH(CH_3)_2$-4
3e	C_6H_4-OCH_3-4	**3j**	C_6H_4-$C(CH_3)_3$-4

Scheme. Synthesis of bis-(oxadiazolymethyl-thio)methylenepyrimidine-dione **3 a–j** derivatives. Reagents and conditions: (i) Et_3N, DMSO, rt (ii) substituted Benzyl halides, K_2CO_3, DMF

triethylamine and dimethyl sulfoxide, it afforded the corresponding 5-(bis((5-phenyl-1,3,4-oxadiazol-2-yl)-methylthio)methylene)-dihydro-2-thioxopyrimidine-4,6-(1*H*,5*H*)-dione **(2)**. Finally, 5-(bis((5-phenyl-1,3,4-oxadiazol-2-yl) methyl-thio)methylene)-2-(4-substitutedbenzylthio)-pyrimidine-4,6-(1*H*,5*H*)-dione derivatives **(3 a–j)** were synthesized by the reaction of **(2)**, substituted benzyl halides and potassium carbonate in DMF solution.

The compound **2** structural assignment was proven by spectroscopic analyses. Its LCMS mass spectrum showed m/z 537 (M + H). ^{1}H NMR (DMSO-d_6) showed protons at δ 11.58 ppm due to 2NH protons and at δ 4.60 ppm due to CH_2 protons. The IR spectrum showed 3235 cm^{-1} due to NH, 1660 cm^{-1} due to CONH and 1490 cm^{-1} due to C = S. The target molecules **(3 a–j)** were also proved by its analytical and spectral analyses. ^{1}H NMR (DMSO-d_6) showed proton regions at δ 11.58 to 11.68, δ 4.58 to 5.20 ppm due to NH, SCH_2 protons. The IR spectrum showed 3230 to 3245 cm^{-1}, 1652 to 1664 cm^{-1} due to NH, CONH.

Experimental

All reagents and solvents were purchased and used 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. The IR spectra were recorded on a Thermo Nicolet FT-IR spectrometer as KBr pellets. NMR spectra were recorded on a varian 300 MHz spectrometer for ^{1}H NMR. The chemical shifts were reported as ppm downfield, using TMS as an internal standard. The ^{13}C NMR spectra were recorded in $CDCl_3$ / DMSO-d_6 on a Bruker spectrometer operating at 75.5 MHz. LCMS Mass spectra were recorded on a MASPEC low resolution mass spectrometer operating at 70 eV.

5 (Bis{[(5-phenyl-1,3,4-oxadiazol-2-yl)-methyl]thio}methylene)-2-thioxodihydropyrimidine-4,6-(1*H*,5*H*)-dione (2)

To a well-stirred solution of thiobarbituric acid (1 mmol) in dimethyl sulfoxide (10 mL), triethylamine (2.5 mmol) and carbon disulfide (1 mmol) were added in succession. The mixture was stirred for 1 h at room temperature, and then 1,3,4-oxadiazole (2 mmol) in dimethyl sulfoxide (10 mL) was added. The stirring was continued for 4 h at room temperature, the mixture was and poured into ice water (100 mL). The solid obtained was recrystallized from methanol to afford a pure compound.

Mp 147–148 °C; % yield: 70; IR (KBr) cm^{-1}: 3235 (NH), 1660 (CONH), 1639 (C = N), 1622 (C = C), 1490 (C = S); ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.60 (s, 4H, S-CH_2), 7.21–7.60 (m, 10H, ArH), 11.58 (bs, 2H, NH); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 174.8, 165.3, 164.8, 163.5, 158.1, 129.5, 128.7, 127.8, 126.8, 106.1, 38.6; mass (m/z): 537 (M + H, 100%); % elemental anal. (found / calcd.): C 51.32 / 51.48, H 3.04 / 3.01, N 15.57 / 15.66.

5-(Bis((5-phenyl-1,3,4-oxadiazol-2-yl)methylthio)methylene)-2-(4-substitutedbenzylthio)-pyrimidine-4,6-(1*H*,5*H*)-dione derivatives (3 a–j)

An ice-cold solution of 5-(Bis((5-phenyl-1,3,4-oxadiazol-2-yl)-methylthio)methylene)-dihydro-2-thioxopyrimidine-4,6-(1*H*,5*H*)-dione **(2)** (1 mmol) in DMF (4 vol), potassium carbonate (1.5 mmol) and substituted benzyl halides (1.3 mmol) was taken in a 1 litre round-bottomed flask equipped with a magnetic stirrer, and stirred for 1 hour. The residual portion was poured onto crushed ice, neutralized with dilute acid, and the product 5-(bis((5-phenyl-1,3,4-oxadiazol-2-yl)methylthio) methylene)-2-(4-substitutedbenzylthio)-pyrimidine-4,6-(1*H*, 5*H)*-dione derivatives **(3 a–j)** was collected by filtration.

2-(Benzylthio)-5-(bis((5-phenyl-1,3,4-oxadiazol-2-yl)methylthio)methylene)pyrimidine-4,6-(1*H*, 5*H*)-dione (3a): mp 189–191 °C; % yield: 65; IR (KBr) cm^{-1}: 3242 (NH), 1658 (CONH), 1637 (C = N), 1624 (C = C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.58 (s, 4H, S-CH_2), 5.12 (s, 2H, S-CH_2), 7.20–7.95 (m, 15H, ArH), 11.60 (s, 1H, NH); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 195.2, 189.4, 170.4, 168.3, 163.2, 140.5, 130.7, 129.7, 128.9, 128.3, 127.6, 113.1, 45.4, 39.2; Mass (m/z): 627 (M + H, 100%); % elemental anal. (found / calcd.): C 57.38 / 57.48, H 3.41 / 3.52, N 13.15 / 13.43.

5-(Bis((5-phenyl-1,3,4-oxadiazol-2-yl)methylthio)methylene)-2-(4-bromobenzylthio)-pyrimidine-4,6-(1*H*,5*H*)-dione (3b): mp 236–238 °C; % yield: 69; IR (KBr) cm^{-1}: 3239 (NH), 1660 (CONH), 1634 (C = N), 1625 (C = C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.64 (s, 4H, S-CH_2), 5.20 (s, 2H, S-CH_2), 7.30–7.95 (m, 14H, ArH), 11.68 (s, 1H, NH); mass (m/z): 707 (M + 2H, 100%); % elemental anal. (found / calcd.): C 49.85 / 51.05, H 3.11 / 3.03, N 12.11 / 11.91.

5-(Bis((5-phenyl-1,3,4-oxadiazol-2-yl)methylthio)methylene)-2-(4-ethylbenzylthio)-pyrimidine-4,6-(1*H*,5*H*)-dione (3c): mp 240–242 °C; % yield: 58; IR (KBr) cm^{-1}: 3233 (NH), 1657 (CONH), 1631 (C = N), 1620 (C = C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.19 (t, 3H, CH_3), 2.55 (q, 2H, CH_2), 4.62 (s, 4H, S-CH_2), 5.15 (s, 2H, S-CH_2), 7.20–7.80 (m, 14H, ArH), 11.62 (s, 1H, NH); Mass (m/z): 655 (M + H, 100%); % elemental anal. (found / calcd.): C 58.59 / 58.70, H 4.09 / 4.00, N 12.65 / 12.81.

5-(Bis((5-phenyl-1,3,4-oxadiazol-2-yl)methylthio) methylene)-2-(4-methylbenzylthio)-pyrimidine-4,6-(1*H*,5*H*)-dione (3d): mp 263–265 °C; % yield: 71; IR (KBr) cm^{-1}: 3231 (NH), 1658 (CONH), 1631 (C = N), 1625 (C = C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.41 (s, 3H, CH_3), 4.60 (s, 4H, S-CH_2), 5.16 (s, 2H, S-CH_2), 7.15–7.75 (m, 14H, ArH), 11.62 (s, 1H, NH); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 193.2, 188.4, 170.5, 167.2, 163.5, 140.2, 132.1, 130.2, 129.5, 128.2, 127.2, 114.1, 44.4, 37.2, 24.9; mass (m/z): 641 (M + H, 100%); % elemental anal. (found / calcd.): C 57.96 / 58.11, H 3.71 / 3.80, N 12.99 / 13.15.

5-(Bis((5-phenyl-1,3,4-oxadiazol-2-yl)methylthio)methylene)-2-(4-methoxybenzylthio)-pyrimidine-4,6-(1*H*,5*H*)-dione (3e): mp 168–170 °C; % yield: 84; IR (KBr) cm^{-1}: 3245 (NH), 1655 (CONH), 1638 (C = N), 1622 (C = C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.60 (s, 3H, OCH_3), 4.60 (s, 4H, S-CH_2), 5.18 (s, 2H, S-CH_2), 7.18–7.88 (m, 14H, ArH), 11.58 (s, 1H, NH); mass (m/z): 657 (M + H, 100%); % elemental anal. (found / calcd.): C 58.71 / 56.69, H 3.69 / 3.72, N 12.64 / 12.81.

5-(Bis((5-phenyl-1,3,4-oxadiazol-2-yl)methylthio)methylene)-2-(4-chlorobenzylthio)-pyrimidine-4,6-(1*H*,5*H*)-dione (3f): mp 209–210 °C; % yield: 70; IR (KBr) cm^{-1}: 3240 (NH), 1652 (CONH), 1640 (C = N), 1618 (C = C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.62 (s, 4H, S-CH_2), 5.16 (s, 2H, S-CH_2), 7.25–7.93 (m, 14H, ArH), 11.60 (s, 1H, NH); mass (m/z): 661 (M + H, 100%); % elemental anal. (found / calcd.): C 54.39 / 54.50, H 3.05 / 3.18, N 12.79 / 12.73.

5-(Bis((5-phenyl-1,3,4-oxadiazol-2-yl)methylthio)methylene)-2-(4-nitrobenzylthio)-pyrimidine-4,6-(1*H*,5*H*)-dione (3 g): mp 184–185 °C; % yield: 79; IR (KBr) cm^{-1}: 3236 (NH), 1664 (CONH), 1638 (C = N), 1629 (C = C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.64 (s, 4H, S-CH_2), 5.20 (s, 2H, S-CH_2), 7.30–7.94 (m, 14H, ArH), 11.62 (s, 1H, NH); mass (m/z): 672 (M + H, 100%); % elemental anal. (found / calcd.): C 53.61 / 53.70, H 3.01 / 3.12, N 14.42 / 14.55.

5-(Bis((5-phenyl-1,3,4-oxadiazol-2-yl)methylthio)methylene)-2-(4-(dimethylamino)benzyl-thio)pyrimidine-4,6-(1*H*,5*H*)-dione (3h): mp 220–222 °C; % yield: 66; IR (KBr) cm^{-1}: 3248 (NH), 1655 (CONH), 1630 (C = N), 1621 (C = C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.75–2.85 (s, 6H, $2CH_3$), 4.59 (s, 4H, S-CH_2), 5.16 (s, 2H, S-CH_2), 7.20–7.86 (m, 14H, ArH), 11.59 (s, 1H, NH); Mass (m/z): 670 (M + H, 100%); % elemental anal. (found / calcd.): C 58.51 / 57.38, H 4.06 / 4.08, N 14.58 / 14.65.

5-(Bis((5-phenyl-1,3,4-oxadiazol-2-yl)methylthio) methylene)-2-(4-isopropylbenzylthio)-pyrimidine-4,6-(1*H*,5*H*)-dione (3i): mp 231–232 °C; % yield: 80; IR (KBr) cm^{-1}: 3230 (NH), 1659 (CONH), 1631 (C = N), 1620 (C = C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.95–1.10 (d, 6H, $2CH_3$), 2.45 (m, 1H, CH), 4.60 (s, 4H, S-CH_2), 5.15 (s, 2H, S-CH_2), 7.20–7.75 (m, 14H, ArH), 11.58 (s, 1H, NH); mass (m/z): 669 (M + H, 100%); % elemental anal. (found / calcd.): C 58.43 / 59.26, H 4.18 / 4.22, N 12.60 / 12.57.

5-(Bis((5-phenyl-1,3,4-oxadiazol-2-yl)methylthio)methylene)-2-(4-*tert*-butylbenzylthio)-pyrimidine-4,6-(1*H*,5*H*)-dione (3j): mp 228–229 °C; % yield: 75; IR (KBr) cm^{-1}: 3242 (NH), 1657 (CONH), 1631 (C = N), 1623 (C = C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.95–1.15 (s, 9H, $3CH_3$), 4.58 (s, 4H, S-CH_2), 5.18 (s, 2H, S-CH_2), 7.18–7.84 (m, 14H, ArH), 11.58 (s, 1H, NH); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 193.5, 190.8, 168.4,

166.3, 165.2, 151.1, 134.6, 130.5, 129.5, 128.4, 128.3, 126.6, 124.8, 112.1, 44.4, 42.5, 40.1, 37.2; mass (m/z): 683 (M + H, 100%); % elemental anal. (found / calcd.): C 59.89 / 59.81, H 4.65 / 4.43, N 12.13 / 12.33.

CONCLUSIONS

The new class of heterocyclic compounds – bis-(oxadiazolymethylthio)methylenepyrimidine-diones – was synthesized in a two-step reaction process with a high yield. The structure of the synthesized compounds was determined, and the characteristics of each compound were elucidated.

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5-(BIS((5-FENIL-1,3,4-OKSADIAZOL-2-IL)METILTIO) METILEN)-2-(4-PAKEISTO BENZILTIO)-PIRIMIDIN-4,6-(1*H*,5*H*)-DIONO DARINIŲ SINTEZĖ

S a n t r a u k a

Susintetinti nauji 5-(bis((5-fenil-1,3,4-oksadiazol-2-il)metiltio)-metilen)-2-(4-pakeisto benziltio)-pirimidin-4,6-(1*H*, 5*H*)-diono dariniai. Gauti junginiai apibūdinti ^{1}H BMR, ^{13}C BMR, masių spektrometrijos, IR spektroskopijos ir elementinės analizės metodais.