Synthesis and Structure of Novel Thieno[2,3-*d*]pyrimidine Derivatives Containing 1,3,4-Oxadiazole Moiety

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The reaction of 5-(1-pyrrolyl)-4-methyl-2-phenylthieno[2,3-*d*]pyrimidine carbohydrazide **5** with CS_2 in the presence of pyridine afforded the 6-(2,3-dihydro-2-mercapto-1,3,4-oxadiazol-5-yl)-4-methyl-5-(1-pyrrolyl)-2-phenylthieno[2,3-*d*]pyrimidine **6**, which reacted with methyl iodide in the presence of sodium methoxide to yield the 6-(2-methylthio-1,3,4-oxadiazol-5-yl)-4-methyl-5-(1-pyrrolyl)-2-phenylthieno[2,3-*d*]pyrimidine **7**. The 6-(2-substituted-1,3,4-oxadiazol-5-yl)-2-phenylthieno[2,3-*d*]pyrimidine derivatives **9**, **11** and **13** were obtained by the condensation of 6-(2-methylthio-1,3,4-oxadiazol-5-yl)-2-phenylthieno[2,3-*d*]pyrimidine **7** with appropriate secondary amines. The structure of the new compounds was substantiated from their IR, UV-vis spectroscopy, ^{1}H NMR, mass spectra, elemental analysis and X-ray crystal analysis.

Keywords: Thioxopyrimidine; 1,3,4-Oxadiazole; Thieno[2,3-*d*]pyrimidine; Spectral characteristics; X-ray crystal structure.

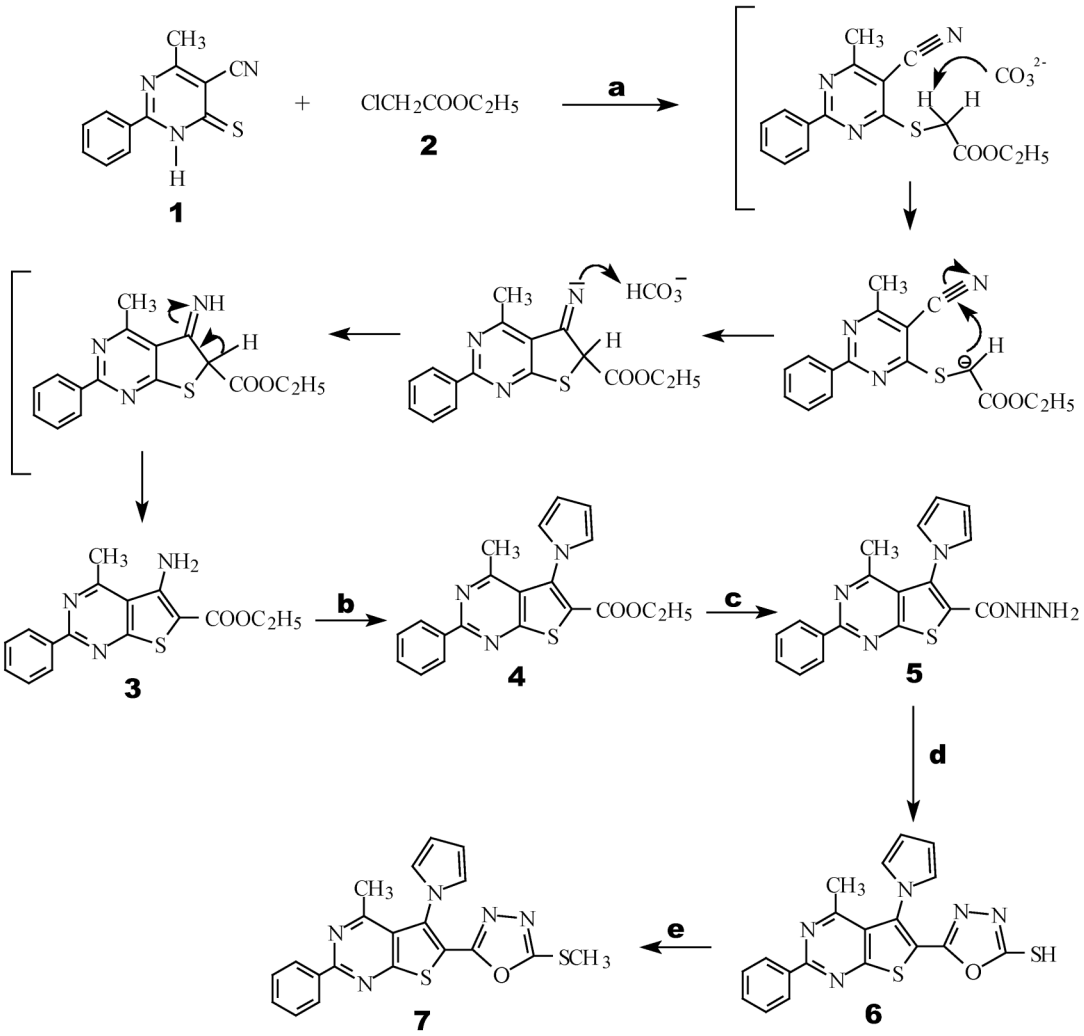
INTRODUCTION

The considerable biological and medicinal activity of fused thienopyrimidines have stimulated much research in this field.[1-5] Likewise, 1,3,4-oxadiazole (OXD) derivatives are useful targets in the search for antivirals as they have been associated with many types of biological properties such as anti-inflammatory,[6,7] antibacterial, antifungal activities,[8,9] and they inhibit HIV replication.[10] The incorporation of two moieties increases biological activity of both and thus it was of value to synthesize some new heterocyclic derivatives having two moieties in the same molecules.Our research has been devoted to the development of new classes of pyrrolothienopyrimidine systems which incorporate the 1,3,4-oxadiazole moiety in the hope that they may be biologically active. In preceding papers[11,12] we have described the synthesis of a series of novel 5-(1-pyrrolyl)-4-methyl-2-phenylthieno[2,3-*d*]pyrimidine derivatives containing chalcones, pyridines, pyridin-2(1H)-ones, 2H-pyran-2-one, pyrazoles, pyrimidines imidazolpyrimidines and pyrazolopyrimidine moiety. In continuation of our studies, we describe the synthesis of some novel thieno-[2,3-*d*]pyrimidine derivatives containing 1,3,4-oxadiazole moiety derived from 5-(1-pyrrolyl)-4-methyl-2-phenylthieno[2,3-*d*]pyrimidine carbohydrazide **5**. The structures of the new compounds were verified by spectroscopic methods and the X-ray crystal structure of compound **9** is also discussed.

RESULTS AND DISCUSSION

All relevant reactions are depicted in Schemes I-II. The required compound 5-cyano-1,6-dihydro-4-methyl-2-phenyl-6-thioxopyrimidine **1** was prepared by treating benzoylisothiocyanate with 3-aminocrotononitrile in refluxing dioxane.[13,14] Cyclization of thioxopyrimidine **1** with ethyl chloroacetate **2** in DMF in the presence of excess anhydrous potassium carbonate at room temperature gave the ethyl 5-amino-4-methyl-2-phenylthieno[2,3-*d*]pyrimidine-6-carboxylate **3** (Scheme I). The possible mechanism for formation of compound **3** can be explained by the reaction pathway depicted in Scheme I. Treatment of compound **3** with 2,5-dimethoxytetrahydrofuran in glacial acetic acid produced the ethyl 5-(1-pyrrolyl)-4-methyl-2-phenylthieno[2,3-*d*]pyrimidine-6-carboxylate **4**, which reacted with an excess of 85% hydrazine hydrate in refluxing ethanol to give the corresponding 5-(1-pyrrolyl)-4-methyl-2-phenylthieno[2,3-*d*]pyrimidine carbohydrazide **5** (Scheme I). The carbohydrazide **5** was used as a key intermediate for the synthesis of novel 1,3,4-oxadiazole-thieno[2,3-*d*]pyrimidine derivatives. The IR spectra of compound **4** indicated the absence of the NH_2 group and carbohydrazide **5** showed the characteristic absorption bands at 3398 and 3335 cm^{-1} for the NH_2 group, at 3110 cm^{-1} for the NH group and 1638 cm^{-1} for the C=O group. The ^{1}H NMR spectra ($CDCl_3$) of compounds **4** and **5** revealed two multiplets at δ 6.49-6.35 (2H, m) and 6.81-6.72 (2H, m), which were

Scheme I

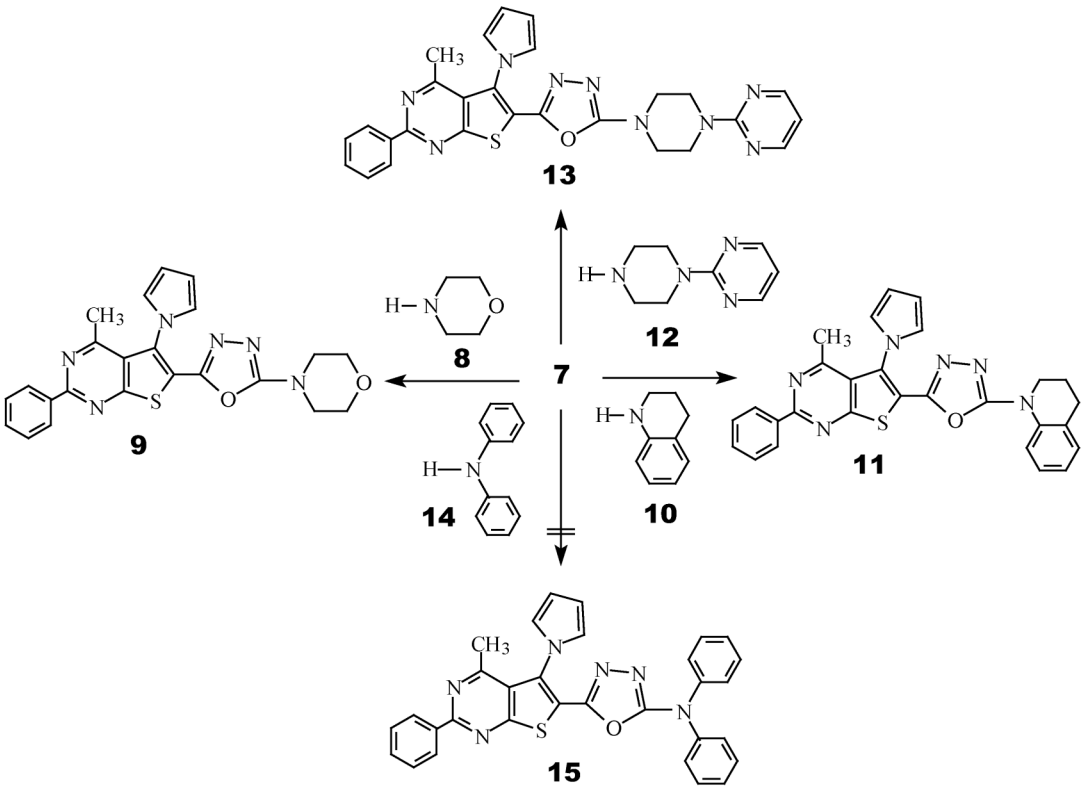


Reagents : (a) DMF/K_2CO_3; (b) 2,5-dimethoxytetrahydrofuran, glacial acetic acid; (c) $NH_2NH_2 \cdot H_2O$; (d) CS_2/pyridine; (e) CH_3I

readily assigned to the hydrogen attached at C_3, C_4 and C_2, C_5 of the pyrrolyl ring, respectively. Moreover, carbohydrazide **5** showed a broad singlet at δ 6.42 (2H, br) assigned to the NH_2 protons and a broad singlet at δ 9.72 (1H, br) assigned to the NH proton.

Next, cyclization of carbohydrazide **5** with CS_2 in the presence of pyridine afforded the 6-(2,3-dihydro-2-mercapto-1,3,4-oxadiazol-5-yl)-4-methyl-5-(1-pyrrolyl)-2-phenylthieno[2,3-*d*]pyrimidine **6** followed by reaction with iodomethane in the presence of sodium methoxide to yield the 6-(2-methylthio-1,3,4-oxadiazol-5-yl)-4-methyl-5-(1-pyrrolyl)-2-phenylthieno[2,3-*d*]pyrimidine **7** (84% yield) (Scheme I). The structures of **6** and **7** were established on the basis of their elemental analysis and spectral data. On the other hand, some novel 6-(2-substituted-1,3,4-oxadiazol-5-yl)-4-methyl-5-(1-pyrrolyl)-2-phenylthieno[2,3-*d*]pyrimidine derivatives **9**, **11** and **13** were also obtained by the condensation reaction of compound **7** with morpholine **8**, 1,2,3,4-tetrahydroquinoline **10** and 1-(2-pyrimidyl)piperazine **12**, respectively (Scheme II). Nevertheless, under the same reaction conditions, reaction of carbohydrazide **5** with N,N-diphenylamine **14** did not produce the desired compound **15**, but led only to the recovery of starting material. Typical proton chemical shift assignment

Scheme II



for compound **11** is shown in Fig. 1. This structure gets further support from mass spectroscopy. It has been observed that electron impact (EI) spectral has many common features. Compounds **9**, **11** and **13** exhibited *m/z* 357, *m/z* 331, *m/z* 315, *m/z* 288, *m/z* 260 and *m/z* 222 piece peaks. The possible mass fragmentation pathway of compound **9** is shown in Chart I.

Furthermore, the absorption spectral characteristics of the compounds **7**, **9**, **11** and **13** were also studied by UV/vis absorption spectroscopy. The absorption maxima (λ_{max}) of the compounds **7**, **9**, **11** and **13** were measured in ethylacetate and dichloromethane solutions and are shown in Table 1. For compounds **7**, **9**, **11** and **13** in ethyl acetate, absorption maxima in the UV region was in the range of 339 to 356 nm, while in dichloromethane it was 343 to 366 nm. It was also found that their λ_{max} values show a significant increase and are clearly bathochromic shifts when the solvent polarity is increased from ethylacetate to dichloromethane, i.e. a positive solvatochromis, which shows that the compounds molecules are more polar in the excited state than the ground state.[15,16] Compound **7**, as a standard, absorbed at 343 nm (dichloromethane) and substituent effects on the absorption maxima were evaluated compared with this value. The differences of these values are shown by $\Delta\lambda_{max}^{CH_2Cl_2}$. As is apparent in Table 1, all the compounds were bathochromic shifts of 15 to 23 nm caused by introduction of the stronger electron donating substituents (such as morpholine, 1,2,3,4-tetrahydroquinoline and 1-((2-pyrimidyl)piperazine) into oxadiazol-thieno[2,3-*d*]pyrimidine moiety at which there is an electron density decrease[17] that should produce a bathochromic shift of λ_{max}. Moreover, the spectroscopic data also demonstrate that the compound **9**

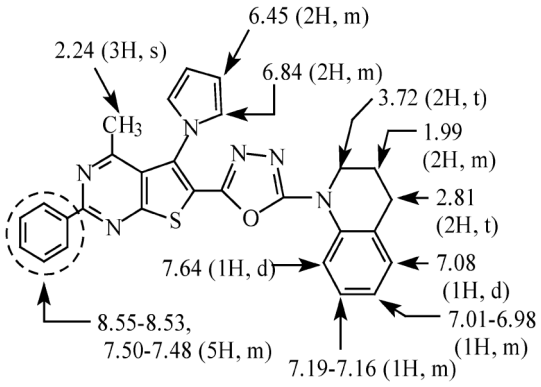
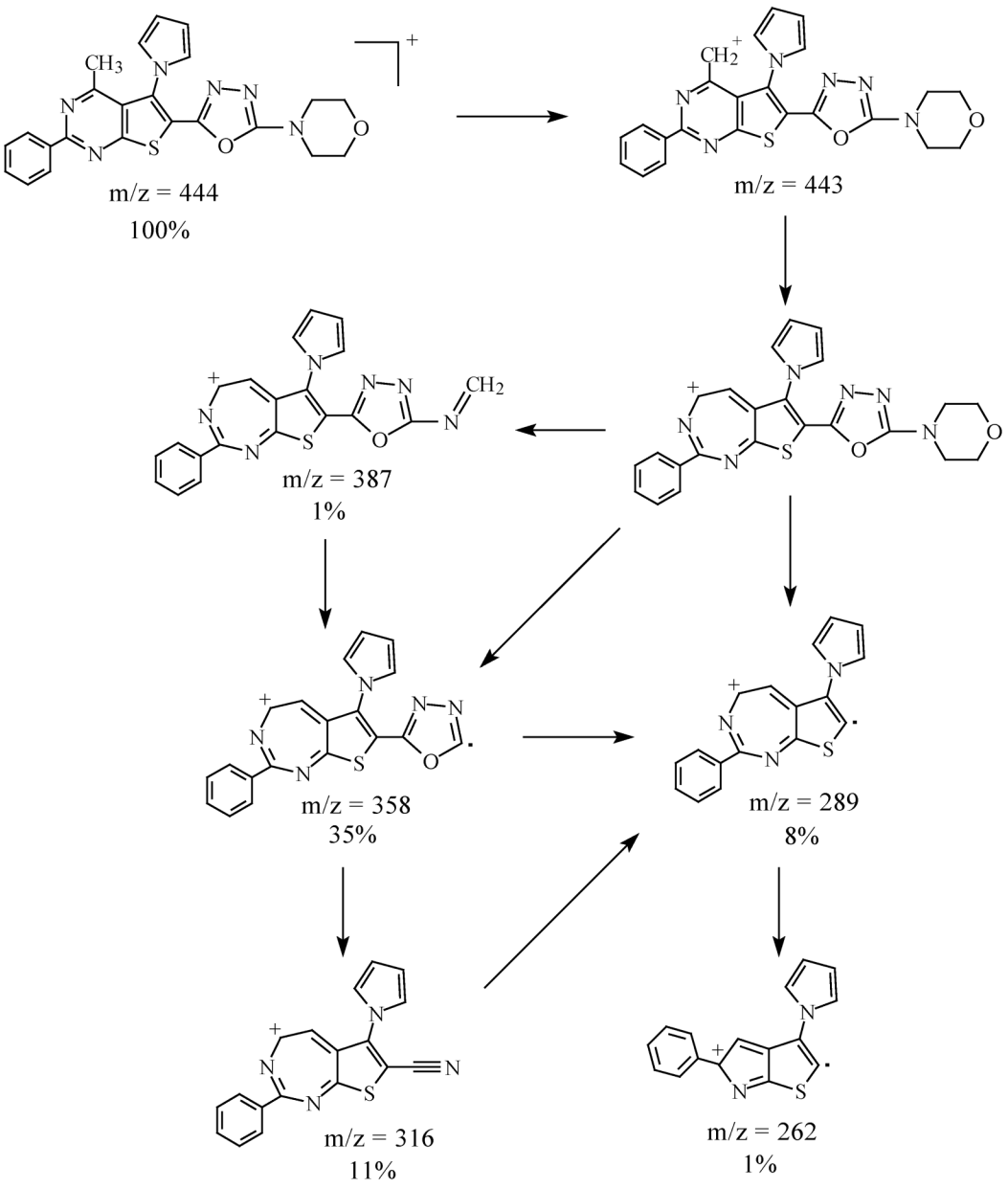


Fig. 1. Typical proton chemical shift assignment for compound **11**.

Chart I

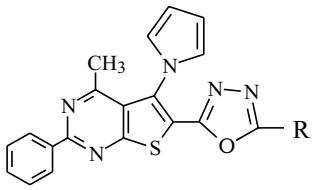


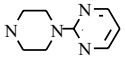
(λ_{max} 366 nm, dichloromethane) containing the morpholinyl group showed the largest bathochromic shift of 23 nm. In general, with respect to the substituents of compounds **7**, **9**, **11** and **13**, the compounds were bathochromically shifted in the order: **9** > **13** > **11** > **7**.

On the other hand, the suitable single crystals of compound **9** were obtained by slow crystallization from chloroform at room temperature. Perspective view and the numbering of the atoms are depicted in Fig. 2. This drawing clearly establishes the structural formula and also shows the conformation of the molecule. The relevant crystallographic date and structure refinement are given in Table 2. The selected bond lengths and bond angles are listed in Table 3. The hydrogen atoms were refined isotropically in idealized positions riding on the atom to which they are attached. The crystal system of compound **9** is monoclinic, the space group is C 2/c and data was collected in the range of 1.67 to 26.01°. Details of the intensity collection are given in Table 2.

The basal plane is formed by phenyl(C(18))-thieno-

Table 1. Absorption spectral date of 6-(2-substituted-1,3,4-oxadiazol-5-yl)-thieno[2,3-*d*]pyrimidine derivatives (**7**, **9**, **11** and **13**)



Compd.	**R**	λ_{max}^{EtOAc} (nm)	$\varepsilon_{max}^{EtOAc}$ (mol^{-1} cm^{-1})	$\lambda_{max}^{CH_2Cl_2}$ (nm)	$\varepsilon_{max}^{CH_2Cl_2}$ (mol^{-1} cm^{-1})	$\Delta\lambda_{max}^{CH_2Cl_2}$
7	SCH_3	339	36192	343	71228	–
9		354	27224	366	33680	23
11		340	23520	358	59280	15
13		356	38672	360	51440	17

^{EtOAc} Measured in ethylacetate; ^{CH_2Cl_2} Measured in dichloromethane

$\Delta\lambda_{max}$: Substituent effects in λ_{max}

[2,3-*d*]pyrimidine(C(9)), thieno[2,3-*d*]pyrimidine(C(7))-oxadiazole(C(6)) and oxadiazole(C(5))-morpholine (N(1)) atoms, with bond lengths of 1.473(4), 1.433(4) and 1.333(4) Å, respectively. The morpholine moiety is in the *trans* (E) configuration with respect to the S atom of the fused thieno-[2,3-*d*]pyrimidine system (Fig. 2). Moreover, the fused thieno[2,3-*d*]pyrimidine system is almost plannar, and due to the effect of thieno[2,3-*d*]pyrimidine moiety, the phenyl group exhibits a noticeable quinoid character that is demonstrated by the shortening of the C(22)-C(23) [1.389(5) Å] and C(19)-C(20) [1.370(4) Å] bond lengths compared to the standard C_{ar}-C_{ar} distance of 1.397(1) Å.[18] In addition, the morpholine and thieno[2,3-*d*]pyrimidine moieties are

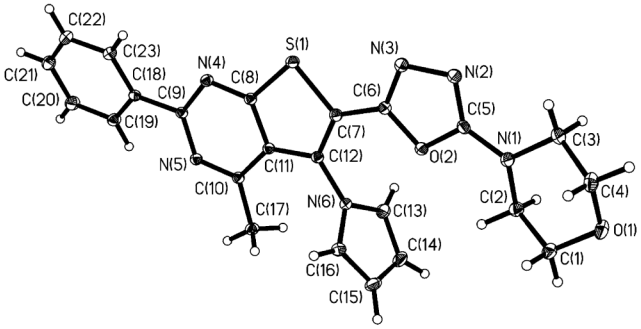


Fig. 2. Perspective view of compound **9** with atomic numbering.

in a staggered conformation with respect to the nitrogen atoms giving rise to some angular distortion at C(5) and C(6) [N(2)-C(5)-N(1) > O(2)-C(5)-N(1) and N(3)-C(6)-C(7) > O(2)-C(6)-C(7)] (Table 3). Similar results are observed in the case of thieno[2,3-d]pyrimidine and phenyl moieties which resulted in angular distortion at C(9) [N(4)-C(9)-C(18) > N(5)-C(9)-C(18)]. The C(5)-N(1) [1.333(4) Å] bond is shorter than the C(6)-C(7) [1.433(4) Å], which is probably due to the electron donating effect of the morpholinly group. Also, the interesting torsion angles which entirely define the molecule conformation are selected and listed in Table 4.

Computation of the oxadiazole plane comprising atoms N(2), N(3), C(6), O(2) and C(5) show that the oxadiazole moiety is almost planar. The planarity is further supported by the conformational angles N(2)-N(3)-C(6)-O(2) (0.4°); N(3)-C(6)-O(2)-C(5) (0.8°); C(6)-O(2)-C(5)-N(2) (-1.8°) and O(2)-C(5)-N(2)-N(3) (2.1°). Moreover, the N(2)-C(5) [1.302(4) Å] bond is a little longer than the N(3)-C(6) [1.291(3) Å]. The N(1)-C(3) morpholine ring has a dihedral angle with an N(2)-N(3) 1,3,4-oxadiazole ring of 15.3°, while the C(7)-S(1) thieno[2,3-*d*]pyrimidine ring's dihedral angle with this 1,3,4-oxadiazole is 1.8°. Furthermore, the pyrrole ring attached to the thieno[2,3-*d*]pyrimidine ring is not coplanar with this ring and makes a

Table 2. Crystal data and structure refinement for compound **9**

Empirical formula	$C_{25}H_{22}N_6O_2S$
Formula weight	486.58
Temperature	297(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	C 2/c
Unit cell dimensions	a = 26.0462(14) Å
	b = 13.6533(7) Å
	c = 13.9836(8) Å
	α = 90°
	β =110.9450(10)°
	γ = 90°
Volume	4644.2(4) Å^3
Z	8
Density (calculated)	1.392 Mg/m^3
Absorption coefficient	0.221 mm^{-1}
Crystal size	0.60 × 0.59 × 0.31 mm
Theta range for data collection	1.67 to 26.01°
Index ranges	$-32 \le h \le 31$, $-16 \le k \le 14$, $-17 \le l \le 10$
Reflections collected	12895
Independent reflections	4564 [R(int) = 0.0263]
Completeness to theta = 26.01°	99.8%
Absorption correction	Empirical
Max. and min. transmission	0.934 and 0.876
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	4564/0/312
Goodness-of-fit on F^2	1.373
Final R indices [I > 2 sigma(I)]	R1 = 0.0672, wR2 = 0.2345
R indices (all data)	R1 = 0.0787, wR2 = 0.2526
Largest diff. peak and hole	1.050 and -0.654 e.Å^{-3}

dihedral angle of 98.1° with the thieno[2,3-*d*]pyrimidine ring plane.

In conclusion, a novel synthesis of some new thieno-[2,3-*d*]pyrimidine derivatives containing 1,3,4-oxadiazole moiety were obtained by the condensation of 6-(2-methylthio-1,3,4-oxadiazol-5-yl)-2-phenylthieno[2,3-*d*]pyrimidine with appropriate secondary amines. The structures of all new synthesized compounds were established from their spectral data, elemental analysis and X-ray crystal analysis. The solvatochromic behaviours and substituent effects in ethyl acetate and dichloromethane solutions were evaluated. The results indicated that the oxadiazol-thieno-[2,3-*d*]pyrimidine derivatives show a significant increase and are clearly bathochromic shifts with an increase in solvent polarity. Moreover, the introduction of electron donating substituents into the oxadiazol-thieno[2,3-*d*]pyrimidine moiety λ_{max} shifts bathochromically in all solvents used.

Table 3. Selected bond lengths [Å] and angles [°] for compound **9**[a]

S(1)-C(7)	1.747(3)	N(1)-C(5)	1.333(4)
N(1)-C(3)	1.448(4)	N(1)-C(2)	1.475(4)
N(2)-C(5)	1.302(4)	N(2)-N(3)	1.390(3)
N(3)-C(6)	1.291(3)	C(6)-C(7)	1.433(4)
C(7)-C(12)	1.359(4)	C(9)-C(18)	1.473(4)
C(19)-C(20)	1.370(4)	C(22)-C(23)	1.389(5)
N(6)-C(16)	1.369(4)	N(6)-C(13)	1.375(4)
N(6)-C(12)	1.423(3)	C(13)-C(14)	1.349(5)
C(14)-C(15)	1.395(5)	C(15)-C(16)	1.359(5)
C(5)-O(2)-C(6)	102.3(2)	N(2)-C(5)-N(1)	129.4(3)
N(1)-C(5)-O(2)	117.7(2)	N(3)-C(6)-C(7)	127.7(3)
O(2)-C(6)-C(7)	120.4(2)	C(12)-C(7)-C(6)	130.2(3)
C(6)-C(7)-S(1)	116.8(2)	N(4)-C(9)-C(18)	117.3(2)
N(5)-C(9)-C(18)	116.8(2)	C(19)-C(18)-C(9)	121.8(2)
C(23)-C(18)-C(9)	120.1(2)	C(5)-N(1)-C(2)	121.4(2)
C(16)-N(6)-C(13)	109.2(2)	C(13)-N(6)-C(12)	124.8(2)
C(14)-C(13)-N(6)	107.3(2)	C(13)-C(14)-C(15)	108.3(2)

[a] Standard deviations in parentheses

Table 4. Selected torsion angles for compound **9**

S(1)-C(7)-C(6)-N(3)	0.9°	S(1)-C(7)-C(6)-O(2)	-179.7°
N(2)-C(5)-N(1)-C(3)	8.1°	N(2)-C(5)-N(1)-C(2)	-164.3°
N(4)-C(9)-C(18)-C(23)	-17°	N(4)-C(9)-C(18)-C(19)	164.5°
C(13)-N(6)-C(12)-C(7)	-82°	C(13)-N(6)-C(12)-C(11)	97.1°

EXPERIMENTAL SECTION

All melting points are uncorrected and in °C. IR spectra were recorded on a JASCO FTIR-3 spectrometer (KBr); ^{1}H NMR spectra were obtained on a Bruker AM-300 WB FI-NLR spectrometer, and chemical shifts are expressed in δ ppm using TMS as an internal standard. Electron impact mass spectra were obtained at 70 eV using a Finingan Mat TSQ-46C spectrometer. Microanalyses for C, H, and N were performed on a Perkin-Elmer 240 elemental analyzer. Electronic spectra were recorded on a Shimadzu UV 240 from compound solutions in ethyl acetate and dichloromethane at a concentration of 1.25×10^{-5} mol liter^{-1}.

Ethyl 5-amino-4-methyl-2-phenylthieno[2,3-*d*]pyrimidine-6-carboxylate (3)

A mixture of 5-cyano-1,6-dihydro-4-methyl-2-phenyl-6-thioxopyrimidine **1** (2.27 g, 0.01 mol), potassium carbonate anhydrous (2.76 g, 0.02 mol) and ethyl chloroacetate **2** (1.23 g, 0.01 mol) in DMF (50 mL) was stirred at room temperature for 4 h and then diluted with cold water (50 mL). The resulting solid product was collected by filtration, washed with water and recrystallized from ethyl ac-

etate/ethanol to give 2.88 g of pale yellow needles (92% yield), mp 177 °C; IR: ν 3488, 3359 (NH_2), 1663 (CO) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.41 (3H, t, J = 4.80 Hz, CH_3), 2.98 (3H, s, CH_3), 4.37 (2H, q, J = 3.0 Hz, OCH_2), 6.23 (2H, br, NH_2), 8.55-8.53, 7.53-7.48 (5H, m, phenyl-H); MS (*m/z*, %): 313 (M^+,100). Anal. Calcd. for $C_{16}H_{15}N_3O_2S$: C, 61.34; H, 4.79; N, 13.41. Found: C, 61.23; H, 4.70; N, 13.41%.

Ethyl 5-(1-pyrrolyl)-4-methyl-2-phenylthieno[2,3-*d*]-pyrimidine-6-carboxylate (4)

A mixture of ethyl 5-amino-4-methyl-2-phenylthieno-[2,3-*d*]pyrimidine-6-carboxylate **3** (3.13 g, 0.01 mol) and 2,5-dimethoxytetrahydrofuran (1.26 g, 0.01 mol) in glacial acetic acid (20 mL) was refluxed for 12 h. After cooling, the resultant solid product was collected by filtration and washed with water, and the crude product recrystallized from ethanol/glacial acetic acid gave 3.16 g of gray white needles (87% yield), mp 165 °C; IR: ν 1697 (CO) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.15 (3H, t, J = 2.0 Hz, CH_3), 2.18 (3H, s, CH_3), 4.18 (2H, q, J = 2.0 Hz, OCH_2), 6.35 (2H, m, 3,4-H of pyrrolyl), 6.72 (2H, m, 2,5-H of pyrrolyl), 8.48-8.46, 7.43-7.42 (5H, m, phenyl-H); MS (*m/z*, %): 363 (M^+, 83), 334 (82), 316 (100), 288 (58), 278 (38), 214 (2), 185 (14), 160 (10), 116 (9), 77 (9), 51 (5). Anal. Calcd. for $C_{20}H_{17}N_3O_2S$: C, 66.11; H, 4.68; N, 11.57. Found: C, 66.13; H, 4.72; N, 11.45%.

4-Methyl-5-(1-pyrrolyl)-2-phenylthieno[2,3-*d*]pyrimidine carbohydrazide (5)

A mixture of compound **4** (3.63 g, 0.01 mol) and hydrazine hydrate (10 mL, 85% solution) was refluxed in absolute ethanol (20 mL) for 24 h. After cooling, the resultant solid product was collected by filtration and washed with water, and the crude product recrystallized from ethanol to give 3.42 g of gray white needles (98% yield), mp 230 °C; IR: ν 3398, 3335 (NH_2), 3110 (NH), 1638 (CO) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.10 (3H, s, CH_3), 6.46 (2H, br, NH_2), 6.49 (2H, m, 3,4-H of pyrrolyl), 6.81 (2H, m, 2,5-H of pyrrolyl), 8.46-8.44, 7.43-7.41 (5H, m, phenyl-H), 9.72 (1H, br, NH); MS (*m/z*, %): 349 (M^+, 39), 318 (100), 289 (9), 277 (26), 244 (8), 212 (2), 187 (6), 160 (8), 116 (9), 104 (5), 77 (7), 69 (2). Anal. Calcd. for $C_{18}H_{15}N_5OS$: C, 61.89; H, 4.29; N, 20.05. Found: C, 61.84; H, 4.22; N, 20.15%.

6-(2,3-Dihydro-2-mercapto-1,3,4-oxadiazol-5-yl)-4-methyl-5-(1-pyrrolyl)-2-phenyl-thieno[2,3-*d*]pyrimidine (6)

A mixture of compound **5** (0.35 g, 1 mmol) and carbondisulphide (5 mL) in pyridine (10 mL) was refluxed on a steam bath for 6 h. After cooling, the resultant solid product was collected by filtration, washed with water and recrystallized from ethanol to give 3.67 g of greenish yellow crystals (94% yield), mp 276 °C; IR: ν 1625 (C=N), 1182 (C=S) cm^{-1}; MS (*m/z*, %): 391 (M^+, 100). Anal. Calcd. for $C_{19}H_{13}N_5OS_2$: C, 58.31; H, 3.32; N, 17.90. Found: C, 58.33; H, 3.23; N, 17.77%.

6-(2-Methylthio-1,3,4-oxadiazol-5-yl)-4-methyl-5-(1-pyrrolyl)-2-phenylthieno[2,3-*d*]pyrimidine (7)

To a mixture of compound **6** (0.39 g, 1 mmol) in methanol (10 mL) and sodium methoxide (0.08 g, 1.5 mmol), iodomethane (0.17 g, 1.2 mmol) was added. After stirring at room temperature for 24 h, the resultant solid product was collected by filtration, washed with water and recrystallized from THF to give 0.34 g of pale yellow crystals (84% yield), mp 215 °C; IR: ν 1625 (C=N) cm^{-1}; ^1H NMR (CF_3COOD): δ 2.53 (3H, s, CH_3), 2.93 (3H, s, SCH_3), 6.23 (2H, m, 3,4-H of pyrrolyl), 7.08 (2H, m, 2,5-H of pyrrolyl), 8.44, 7.76-7.73 (5H, m, phenyl-H); MS *(m/z*, %): 405 (M^+, 100), 358 (12), 331 (38), 315 (20), 304 (53), 289 (18), 261 (8), 244 (2), 198 (10), 151 (4), 103 (3), 75 (4). Anal. Calcd. for $C_{20}H_{15}N_5OS_2$: C, 59.25; H, 3.70; N, 17.28. Found: C, 59.13; H, 3.55; N, 17.33%.

6-(2-Substituted-1,3,4-oxadiazol-5-yl)-4-methyl-5-(1-pyrrolyl)-2-phenylthieno[2,3-*d*]pyrimidine derivatives (9, 11 and 13) General procedure:

A mixture of compound **7** (0.405 g, 1 mmol) and excess secondary amines **8**, **10** and **12** (morpholine, 1,2,3,4-tetrahydroquinoline and 1-((2-pyrimidyl)piperazine) (5 mmol) was refluxed for 10 h and poured into ice-water, and the precipitated product was collected by filtration, washed with water, and the crude product recrystallized from chloroform/THF.

6-(2-Morpholinyl-1,3,4-oxadiazol-5-yl)-4-methyl-5-(1-pyrrolyl)-2-phenylthieno[2,3-*d*]pyrimidine (9)

Yield 90%, mp 281 °C; IR: ν 1611 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.52 (3H, s, CH_3), 3.86 (4H, d, J = 1.0 Hz, 2,6-H of morpholinyl), 4.17 (4H, d, J = 1.0 Hz, 3,5-H of morpholinyl), 6.78 (2H, m, 3,4-H of pyrrolyl), 7.10 (2H, m, 2,5-H of pyrrolyl), 8.49-8.47, 7.90-7.86 (5H, m, phenyl-H); MS (*m/z*, %): 444 (100), 387 (1), 357 (35), 331 (10), 315 (11), 301 (81), 288 (8), 275 (1), 262 (1), 222 (12), 196 (8), 164 (2), 151 (4), 117 (12), 68 (16). Anal. Calcd. for $C_{23}H_{20}N_6O_2S$: C, 62.16; H, 4.50; N, 18.91. Found: C, 62.29; H, 4.41; N, 19.01%.

6-(2-Quinolizinyl-1,3,4-oxadiazol-5-yl)-4-methyl-5-(1-pyrrolyl)-2-phenylthieno[2,3-*d*]pyrimidine (11)

Yield 56%, mp 185 °C; IR: ν 1602 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.01-1.98 (2H, m, 3-H of quinolizinyl), 2.24 (3H, s, CH_3), 2.81 (2H, t, *J* = 1.28 Hz, 4-H of quinolizinyl), 3.72 (2H, t, *J* = 1.25 Hz, 2-H of quinolizinyl), 6.45 (2H, m, 3,4-H of pyrrolyl), 6.84 (2H, m, 2,5-H of pyrrolyl), 7.01-6.98 (1H, m, 6-H of quinolizinyl), 7.08 (1H, d, *J* = 1.0 Hz, 5-H of quinolizinyl), 7.19-7.16 (1H, m, 7-H of quinolizinyl), 7.64 (1H, d, *J* = 1.0 Hz, 8-H of quinolizinyl), 8.55-8.53, 7.50-7.48 (5H, m, phenyl-H); MS (*m/z*, %): 490 (100), 438 (5), 405 (44), 358 (18), 331 (41), 315 (52), 302 (60), 288 (28), 278 (10), 261 (11), 245 (39), 198 (22), 160 (29), 128 (20), 133 (78), 117 (7), 77 (4). Anal. Calcd. for $C_{28}H_{22}N_6OS$: C, 68.57; H, 4.48; N, 17.14. Found: C, 68.88; H, 4.59; N, 17.38%.

6-(2-Piperazinyl-1,3,4-oxadiazol-5-yl)-4-methyl-5-(1-pyrrolyl)-2-phenylthieno[2,3-*d*]pyrimidine (13)

Yield 58%, mp 307 °C; IR: ν 1606 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.26 (3H, s, CH_3), 3.43 (4H, d, *J* = 1.05 Hz, 2,6-H of piperazinyl), 3.89 (4H, d, *J* = 1.02 Hz, 3,5-H of piperazinyl), 6.43 (2H, t, *J* = 4.00 Hz, 3,4-H of pyrrolyl), 6.57 (1H, m, 5-H of pyrimidinyl), 6.84 (2H, t, *J* = 4.10 Hz, 2,5-H of pyrrolyl), 9.35 (2H, d, *J* = 1.0 Hz, 4,6-H of pyrimidinyl), 8.56-8.54, 7.51-7.49 (5H, m, phenyl-H); MS (*m/z*, %): 521 (50), 506 (1), 426 (3), 400 (21), 387 (10), 358 (11), 331 (18), 315 (72), 302 (45), 288 (21), 275 (5), 261 (20), 243 (6), 228 (2), 212 (8), 199 (23), 188 (26), 163 (52), 134 (100), 120 (41), 108 (31), 80 (15), 117 (7), 77 (4). Anal. Calcd. for $C_{27}H_{23}N_9OS$: C, 62.18; H, 4.41; N, 24.18. Found: C, 62.36; H, 4.59; N, 24.33%.

X-ray structure study of compound 9

The diffraction data of compound **9** was collected on a Siemens CCD diffractometer, which was equipped with graphite-monochromated Mo-K_α (K_α = 0.71073 Å) radiation. Data reduction was carried out by standard methods with use of well-established computational procedures.[19] A pale yellow crystal of **9** was mounted on the top of a glass fiber with epoxy cement. The hemisphere data collection method was used to scan the data points at $3.34 < 2\theta < 52.02°$. The structure factors were obtained after Lorentz and polarization corrections. The final residuals of the final refinement were R1 = 0.0672, wR2 = 0.2345. The crystallographic data of compound **9** has been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC 695659. A copy of this information may be obtained free of charge via http://www.ccdc.cam.ac.uk or from The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +441223/336-033; e-mail: deposit@ccdc.cam.ac.uk).

ACKNOWLEDGEMENT

We are grateful to the National Science Council of Taiwan for their financial support.

Received October 17, 2008.

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