Heteroatom Chemistry
Volume 19, Number 1, 2008

Synthesis, Structure, and Biological Activity of Novel 4,5-Disubstituted Thiazolyl Urea Derivatives

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Received 1 July 2006; revised 14 October 2006

ABSTRACT: *Novel 1-(2,4-dichlorophenyl)-3-[4-aryl-5-(1*H*-1,2,4-triazol-1-yl)thiazol-2-yl] urea derivatives were synthesized by the reaction of 2-amino-4-sustituted phentyl-5-(1*H*-1,2,4-triazol-1-yl) thiazoles with 2,4-dichloro-1-isocyanatobenzene. Structures of the title compounds were confirmed by the elemental analysis, ^{1}H NMR, and single crystal X-ray diffraction analysis. Biological evaluation showed that some of them possess promising antitumor activities.* © 2008 Wiley Periodicals, Inc. Heteroatom Chem 19:2–6, 2008; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20375

INTRODUCTION

Thiazole derivatives were reported to exhibit diversely biological activities, such as antitumor, antituberculous, and fungicide activity [1,2]. Paolo et al. disclosed that 2-ureido-1,3-thiazole derivatives were active as cyclin-dependent kinase (CDK)/cyclin inhibitors, which were useful for treating cell proliferative disorders associated with an altered cell-dependent kinase activity [3].

Up to now, 1,2,4-triazole derivatives have been found to be active compounds with therapeutic nature, such as antiseptic [4,5], analgesic [6], antitumor [7], antiasthmatic, diuretic, hypotensive effects [8], and anti-inflammatory [9]. As a continuation of our studies on triazole derivatives [5–7], we have sought to synthesize novel thialoyl urea compounds incorporating 1*H*-1,2,4-triazole units and in search of novel leading compounds with potential anticancer activities. We herein report the synthesis and structures of a series of novel 1-(2,4-dichlorophenyl)-3-[4-aryl-5-(1*H*-1,2,4-triazol-1-yl)thiazol-2-yl]urea, which has been characterized by spectral data and crystal X-ray diffraction analysis. These compounds were also evaluated for their in vitro anticancer activity.

RESULT AND DISCUSSION

Synthesis

Compounds **1** were synthesized from the reaction of α-bromo-substituted acetophenone and thiourea [13] by the Hantzsh reaction. 2-Amino-4-sustituted phentyl-5-(1*H*-1,2,4-triazol-1-yl)thiazole (**1a–m**) were heated with 2,4-dichloro-1-isocyanatobenzene in anhydrous toluene to obtain 1-(2,4-dichlorophenyl)-3-[4-aryl-5-(1*H*-1,2,4-triazol-1-yl)thiazol-2-yl]ureas (**3a–m**) (Scheme 1).

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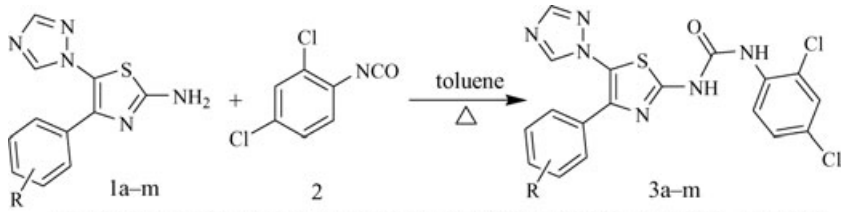
Contract grant sponsor: National Natural Science Foundation of China.
Contract grant number: 20172030.
Contract grant sponsor: Key Project of Chinese Ministry of Education.
Contract grant number: 105046.



SCHEME 1

Structure

Figure 1 shows the molecular structure of **3m** that contains the following four planar subunits: the thiazole ring (P1), the triazole ring (P2), 2,3,4-trichlorophenyl ring C5–C10 (P3), and 2,4-dichlorophenyl C13–C18 (P4). The dihedral angles between P1 and P2, P3, P4 are 60.4, 74.6 and 11.5°, respectively. In the crystal structure, weak intermolecular C—H···O interaction (Fig. 2) is found [C(15)—H(15)···O(1): C—H = 0.93 Å, H···O = 2.489 Å, C···O = 3.366 Å, and C(15)—H(15)···O(1) = 163.4°; symmetry code: (i) $-x + 1, -y, -z + 1$].

Biological Activity

Compounds **3** were evaluated for their anticancer potency in vitro against four human cell lines, including HL-60 leukemia, BGC-823 gastric carcinoma, Bel-7402 liver cancer, and KB nasopharyngeal cancer cell lines and adopted MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] and SRB (sulforhodamin B) assay. The result of inhibition percentage of human tumor cell lines in the presence of compounds **3** in DMSO is presented in Table 1. Compounds **3k, 3l**, and **3m** were found to have good cytotoxic activities against all four human tumor cell lines on the tested concentrations (10 μM). Furthermore, compounds **3c, 3d**, and **3g** showed good anticancer activity against gastric cancer cell line with 78.18%, 80.67%, and 72.58% inhibition ratio percentage, respectively. Compound **3l** showed good activity against liver cancer cell line with a 90.11% inhibition ratio percentage.

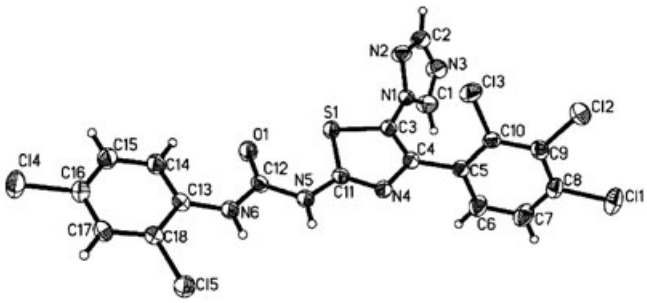


FIGURE 1 A view of **3m** with the atom-numbering scheme and 30% probability displacement ellipsoids. Selected bond lengths (Å): S(1)–C(1) 1.733(2); Cl(1)–C(8) 1.728(3); Cl(2)–C(9) 1.715(3); Cl(3)–C(10) 1.726(2); Cl(4)–C(16) 1.748(3); Selected bond angles (°): C(4)–C(3)–N(1) 127.9(2); N(4)–C(11)–N(5) 120.4(2); C(3)–C(4)–C(5) 127.3(2); N(6)–C(12)–N(5) 112.0(2); C(12)–N(6)–C(13) 127.5(2); C(11)–S(1)–C(3) 86.97(11).

SUMMARY

To summarize, we synthesized a series of 2-amino-1,3-thiazole containing 1*H*-1,2,4-triazole derivatives **3a–m**, and their structures were established on the basis of ^{1}H NMR spectral data and elemental analysis. Finally, the structure of compound **3m** was confirmed by X-ray crystallographic studies. These novel 2-amino-1,3-thiazole derivatives had also been screened for their in vitro anticancer activity against four human cancer cell lines. The results showed that some compounds of **3** have good cytotoxic activity.

EXPERIMENTAL

Melting points (°C) were determined by X-4 digital melting point apparatus, which are uncorrected. The ^{1}H NMR spectra were measured on a

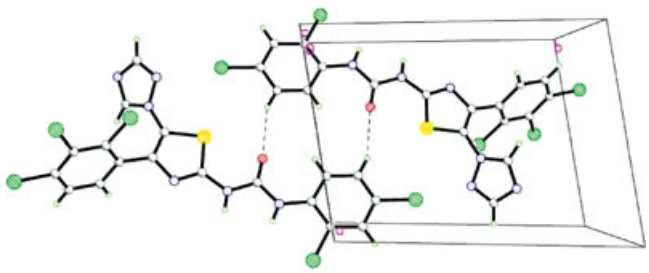


FIGURE 2 A packing diagram for **3m.**

TABLE 1 Inhibition Percentages of Four Human Tumor Cell Lines in the Presence of Compounds **3**

		Ratio of Inhibition (%; 10 μmol/L)			
Compound	*R*	*HL-60 (Leukemia) (MTT)*	*BGC-823 (Gastric Cancer) (SRB)*	*Bel-7402 (Liver Cancer) (SRB)*	*KB (Nasopharyngeal KB (Cancer) (SRB)*
3a	H	31.94	22.00	4.77	6.89
3b	4-F	21.74	5.64	−4.40	1.31
3c	2-Cl	57.22	78.18	41.04	49.39
3d	3-Cl	61.04	80.67	17.93	44.95
3e	4-Cl	51.91	2.89	8.60	−5.80
3f	2-Br	66.04	67.15	58.71	54.72
3g	3-Br	67.05	72.58	41.46	67.05
3h	4-Br	54.97	2.74	2.09	−3.44
3i	4-OMe	50.64	4.14	3.59	12.73
3j	2,4-F	27.36	1.44	−5.44	2.40
3k	2,4-Cl	68.14	65.08	75.09	76.63
3l	2,5-Cl	53.55	81.68	90.11	78.43
3m	2,3,4-Cl	69.97	74.59	83.54	76.21

Brucker AC-300 spectrometer in DMSO-d_6 solution with TMS as internal standard. Elemental analysis was determined on a Yanaco CHN corder elemental analyzer. X-ray diffraction data were recorded on a Bruker Smart 1000 diffractometer (graphite-monochromatized Mo Kα radiation, $\lambda = 0.71073$ Å) at 293 K.

*Synthesis of 1-(2,4-Dichlorophenyl)-3-[4-aryl-5-(1H-1,2,4-triazol-1-yl)thiazol-2-yl]Urea (**3a–m**)*

2-Amino-4-sustituted phentyl-5-(1*H*-1,2,4-triazol-1-yl)thiazoles **1** (1 mmol) were refluxed with 2,4-dichloro-1-isocyanatobenzene in anhydrous toluene for 3–8 h (tracked with TLC). Then, the mixture was cooled and filtered to obtain white solid. Compounds **3** were recrystallized from DMF–ethanol or ethanol (**3c** and **3f**) in various yields. The physical properties, elemental analysis data, and ^{1}H NMR spectra data of compound **3** are described below.

1-(2,4-Dichlorophenyl)-3-[4-phenyl-5-(1*H*-1,2,4-triazol-1-yl)thiazol-2-yl]urea (**3a**): White crystal, yield 89.33%, mp 180–183°C, ^{1}H NMR: δ (DMSO-d_6) 8.82 (s, 1H, Tr-H), 8.36 (s, 1H, Tr-H), 8.17 (d, 1H, Ar-H, J= 9 Hz), 7.70–7.69 (d, 1H, Ar-H, J= 2.4 Hz), 7.47–7.43 (q, 1H, Ar-H, J= 2.4 Hz), 7.38–7.35 (m, 3H, Ar-H), 7.26–7. 23 (m, 2H, Ar-H); Anal. Calcd for $C_{18}H_{12}Cl_2N_6OS$: C, 50.13; H, 2.80; N, 19.49; Found C, 50.53; H, 3.09; N, 19.81.

1-(2,4-Dichlorophenyl)-3-[4-(4-fluorophenyl-5-(1*H*-1, 2,4-triazol-1-yl)thiazol-2-yl]urea (**3b)**: White crystal, yield 75.40%, mp 264–268°C, ^{1}H NMR: δ (DMSO-d_6) 8.85 (s, 1H, Tr-H), 8.37 (s, 1H, Tr-H), 8.18 (d, 1H, Ar-H, J= 9 Hz), 7.70–7.69 (d, 1H, Ar-H, J = 2..4 Hz), 7.47–7.43 (q, 1H, Ar-H, J= 2.4 Hz), 7.31–7.17 (m, 4H, Ar-H); Anal. Calcd for $C_{18}H_{11}Cl_2FN_6OS$: C, 48.12; H, 2.47; N, 18.71; Found C, 47.99; H, 2.38; N, 18.59.

1-(2,4-Dichlorophenyl)-3-[4-(2-chlorophenyl-5-(1*H*-1,2,4-triazol-1-yl)thiazol-2-yl]urea (**3c)**: White crystal, yield 71.43%, mp 223–226 °C, ^{1}H NMR: δ (DMSO-d_6) 8.49 (s, 1H, Tr-H), 8.18 (s, 1H, Tr-H), 8.19–8.15 (q, 1H, Ar-H, J= 2.7 Hz), 7.70 (d, 1H, Ar-H, J= 2.4 Hz), 7.52–7.40 (m, 5H, Ar-H); Anal. Calcd for $C_{18}H_{11}Cl_3N_6OS$: C, 46.42; H, 2.38; N, 18.04; Found C, 46.42; H, 2.42; N, 17.92.

1-(2,4-Dichlorophenyl)-3-[4-(3-chlorophenyl-5-(1H-1,2,4-triazol-1-yl)thiazol-2-yl]urea (**3d**): White crystal, yield 97.13%, mp 255–258°C, ^{1}H NMR: δ (DMSO-d_6) 8.82 (s, 1H, Tr-H), 8.36 (s, 1H, Tr-H), 8.17 (d, 1H, Ar-H, J= 9 Hz), 7.71 (d, 1H, Ar-H, J= 2.4 Hz), 7.47–7.37 (m, 3H, Ar-H), 7.26 (s, 1H, Ar-H), 7.14 (d, 1H, Ar-H, J= 7.2 Hz); Anal. Calcd for $C_{18}H_{11}Cl_3N_6OS$: C, 46.42; H, 2.38; N, 18.04; Found C, 46.63; H, 2.27; N, 18.10.

1-(2,4-Dichlorophenyl)-3-[4-(4-chlorophenyl-5-(1*H*-1,2,4-triazol-1-yl)thiazol-2-yl]urea (**3e**): White crystal, yield 80.28%, mp 272–275°C, ^{1}H NMR: δ (DMSO-d_6) 8.84 (s, 1H, Tr-H), 8.37 (s, 1H, Tr-H), 8.16 (d, 1H, Ar-H, J= 9 Hz), 7.68 (d, 1H, Ar-H, J= 2.4 Hz), 7.45–7.42 (m, 3H, Ar-H), 7.24 (d, 2H, Ar-H, J= 8.4 Hz); Anal. Calcd for $C_{18}H_{11}Cl_3N_6OS$: C, 46.42; H, 2.38; N, 18.04; Found C, 46.80; H, 2.69; N, 17.62.

1-(2,4-Dichlorophenyl)-3-[4-(2-bromophenyl-5-(1*H*-1,2,4-triazol-1-yl)thiazol-2-yl]urea (**3f**): White crystal, yield 69.64%, mp 215–217°C, ^{1}H NMR: δ (DMSO-d_6) 8.44 (s, 1H, Tr-H), 8.17 (s, 1H, Tr-H), 8.17 (d, 1H, Ar-H, J= 8.7 Hz), 7.71–7.68 (t, 2H, Ar-H), 7.48–7.44 (m, 3H, Ar-H), 7.40–7.34 (m, 1H, Ar-H); Anal. Calcd for $C_{18}H_{11}BrCl_2N_6OS$: C, 42.37; H, 2.17; N, 17.47; Found C, 42.19; H, 2.40; N, 16.32.

1-(2,4-Dichlorophenyl)-3-[4-(3-bromophenyl-5-(1*H*-1,2,4-triazol-1-yl)thiazol-2-yl]urea (**3g**): White crystal, yield 96.43%, mp 250–252°C, ^{1}H NMR: δ (DMSO-d_6) 8.89 (s, 1H, Tr-H), 8.40 (s, 1H, Tr-H), 8.18 (d, 1H, Ar-H, J= 9 Hz), 7.71 (d, 1H, Ar-H, J= 2.4 Hz), 7.56 (d, 1H, Ar-H, J= 8.1 Hz), 7.47–7.41 (m, 2H, Ar-H), 7.36–7.31 (t, 1H, Ar-H), 7.17 (d, 1H, Ar-H, J= 7.8 Hz); Anal. Calcd for $C_{18}H_{11}BrCl_2N_6OS$: C, 42.37; H, 2.17; N, 16.47; Found C, 42.20; H, 2.28; N, 16.56.

1-(2,4-Dichlorophenyl)-3-[4-(4-bromophenyl-5-(1*H*-1,2,4-triazol-1-yl)thiazol-2-yl]urea (**3h**): White crystal, yield 88.89%, mp 257–260°C, ^{1}H NMR: δ (DMSO-d_6) 8.84 (s, 1H, Tr-H), 8.37 (s, 1H, Tr-H), 8.16 (d, 1H, Ar-H, J= 9 Hz), 7.69 (d, 1H, Ar-H, J= 2.4 Hz), 7.58 (d, 2H, Ar-H, J= 8.7 Hz), 7.47–7.43 (q, 1H, Ar-H), 7.17 (d, 2H, Ar-H, J= 8.7 Hz); Anal. Calcd for $C_{18}H_{11}BrCl_2N_6OS$: C, 42.37; H, 2.17; N, 16.47; Found C, 42.20; H, 2.23; N, 16.62.

1-(2,4-Dichlorophenyl)-3-[4-(4-methoxyphenyl-5-(1*H*-1,2,4-triazol-1-yl)thiazol-2-yl]urea (**3i**): White crystal, yield 60.61%, mp 248–250°C, ^{1}H NMR: δ (DMSO-d_6) 8.82 (s, 1H, Tr-H), 8.36 (s, 1H, Tr-H), 8.19 (d, 1H, Ar-H, J= 9 Hz), 7.69 (d, 1H, Ar-H, J= 2.4 Hz), 7.46–7.43 (q, 1H, Ar-H), 7.18 (d, 2H, Ar-H, J= 8.7 Hz), 6.92 (d, 2H, Ar-H, J= 8.7 Hz), 3.75 (s, 3H, OCH_3); Anal. Calcd for $C_{19}H_{14}Cl_2N_6O_2S$: C, 49.47; H, 3.06; N, 18.22; Found C, 49.21; H, 2.99; N, 18.44.

1-(2,4-Dichlorophenyl)-3-[4-(2,4-difluorophe-nyl-5-(1*H*-1,2,4-triazol-1-yl)thiazol-2-yl]urea (**3j**): White crystal, yield 92.73%, mp 256–258°C, ^{1}H NMR: δ (DMSO-d_6) 8.72 (s,1H, Tr-H), 8.23 (s, 1H, Tr-H), 8.16 (d, 1H, Ar-H, J= 9 Hz), 7.69 (d, 1H, Ar-H, J= 2.4 Hz), 7.63–7.55 (m, 1H, Ar-H), 7.48–7.44 (q, 1H, Ar-H), 7.31–7.16 (m, 2H, Ar-H); Anal. Calcd for $C_{18}H_{10}Cl_2F_2N_6OS$: C, 46.27; H, 2.16; N, 17.98; Found C, 45.92; H, 2.49; N, 17.62.

1-(2,4-Dichlorophenyl)-3-[4-(2,4-dichlorophe-nyl-5-(1*H*-1,2,4-triazol-1-yl)thiazol-2-yl]urea (**3k**): White crystal, yield 78.38%, mp 208–211°C, ^{1}H NMR: δ (DMSO-d_6) 8.59 (s,1H, Tr-H), 8.19 (s, 1H, Tr-H), 8.17 (d, 1H, Ar-H, J = 9 Hz), 7.71–7.44 (m, 5H, Ar-H); Anal. Calcd for $C_{18}H_{10}Cl_4N_6OS$: C, 43.22; H, 2.02; N, 16.80; Found C, 43.47; H, 2.40; N, 16.48.

1-(2,4-Dichlorophenyl)-3-[4-(2,5-dichlorophe-nyl-5-(1*H*-1,2,4-triazol-1-yl)thiazol-2-yl]urea (**3l**): White crystal, yield 72.92%, mp 239–241°C, ^{1}H NMR: δ (DMSO-d_6) 8.63 (s,1H, Tr-H), 8.20 (s, 1H, Tr-H), 8.17 (d, 1H, Ar-H, J= 9 Hz), 7.70 (d, 1H, Ar-H, J= 2.4 Hz), 7.59–7.59 (t, 1H, Ar-H), 7.53 (d, 2H, Ar-H, J= 1.8 Hz), 7.48–7.44 (q, 1H, Ar-H); Anal. Calcd for $C_{18}H_{10}Cl_4N_6OS$: C, 43.22; H, 2.02; N, 16.80; Found C, 43.58; H, 2.41; N, 16.46.

TABLE 2 Crystal Data and Structure Refinement for **3m**

Formula	C_{18} H_9 Cl_5 N_6 O_2 S
Formula weight	534.63
Color/shape	Pale yellow/block
Crystal system	Triclinic
Space group	*P*-1
a (Å)	8.7717(13)
b (Å)	11.9918(18)
c (Å)	12.1633(18)
α (°)	77.181(2)
β (°)	87.601(2)
γ (°)	80.631(2)
V (Å^3)	1230.9(3)
Z	2
D (calcd.) (g cm^{-3})	1.567
μ (mm^{-1})	0.706
F(000)	588
Crystal size (mm)	0.24 × 0.20 × 0.18
Temperature (K)	293(2)
θ ranges (°)	1.76–25.00
h/*k*/*l*	−9,10/−14,14/−14,12
Reflections collected	6275
Independent reflections	4316
Absorption correction	Semiempirical
Numbers of restrains/ Numbers of parameters	0/309
Final *R* indices [$I > 2\sigma(I)$]	R_1= 0.0355 wR_2= 0.0895

1-(2,4-Dichlorophenyl)-3-[4-(2,3,4-trichlorophenyl-5-(1*H*-1,2,4-triazol-1-yl)thiazol-2-yl]urea (**3m**): Pale yellow crystal, yield 85.71%, mp: 220–223°C, ^{1}H NMR: δ (DMSO-d_6) 8.66 (s, 1H, Tr-H), 8.20 (s, 1H, Tr-H), 8.17 (d, 1H, Ar-H, J= 9 Hz), 7.74–7.70 (m, 2H, Ar-H), 7.49–7.44 (m, 2H, Ar-H); Anal. Calcd for $C_{18}H_9Cl_5N_6OS$: C, 40.44; H, 1.70; N, 15.72; Found C, 46.81; H, 2.01; N, 15.39.

Crystallographic Measurement

The pale yellow crystals with dimensions 0.24 mm × 0.20 mm × 0.18 mm were mounted on a fiber. The structure was solved by direct methods and completed by difference Fourier map using the SHELXL-97 program, and refined by full-matrix least squares on F^2. The nonhydrogen atoms were refined anisotropically, and hydrogen atoms were added according to the theoretical models. Crystallographic data are listed in Table 2.

Supplementary Material

Crystallographic data for structure **4c** has been deposited in the Cambridge Crystallographic Data Center, CCDC No. 612101. Copies of this information may be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ,

UK (Fax: +44–1223–336033; email: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk.)

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