Available online at www.sciencedirect.com

ScienceDirect

Journal of Fluorine Chemistry 128 (2007) 879–884

JOURNAL OF FLUORINE CHEMISTRY

www.elsevier.com/locate/fluor

A facile synthesis and herbicidal activities of novel fluorine-containing thiazolo[4,5-*d*]pyrimidin-7(6H)-ones

Ying Liang, Shuang Fan, Wen Yan Mo, Hong Wu He *

Key Laboratory of Pesticide & Chemical Biology, Ministry of Education, Central China Normal University, Wuhan, Hubei 430079, PR China

Received 29 March 2007; received in revised form 9 April 2007; accepted 9 April 2007
Available online 19 April 2007

Abstract

Eighteen novel 5-alkylamino-6-aryl-3-phenyl-2-thioxo-2,3-dihydrothiazolo[4,5-*d*]pyrimidin-7(6H)-ones **5a–r** were designed and easily synthesized *via* a tandem aza-Wittig reaction. Treatment of iminophosphorane **2** with aromatic isocyanate gave carbodiimide **3**, which reacted with fluoro-substituted alkylamines to provide the title compounds in 65–87% isolated yields using sodium ethoxide as catalyst. All compounds **5** were confirmed by **IR**, ^{1}H NMR, MS and elemental analysis, and compound **5p** was further analyzed by single-crystal X-ray diffraction. The preliminary bioassay indicated that some compounds showed significant inhibition activities against the root growth of rape and barnyard grass at a dosage of 100 mg/L.

Keywords: Thiazolo[4,5-*d*]pyrimidin-7-one; aza-Wittig reaction; Synthesis; Herbicidal activity

1. Introduction

Thiazolo[4,5-*d*]pyrimidine derivatives, which can be considered as thia-analogues of the natural purine bases such as adenine and guanine, have acquired a growing importance as anticancer agents [1], antiviral agents used in the treatment of human cytomegalovirus [2], antitumour agents [3] and antibacterial agents [4]. However, few reports so far are available on the pesticidal activities of thiazolo[4,5-*d*]pyrimidine derivatives.

In the development of agrochemicals for crop protection, fluorine-containing compounds are widely employed as herbicides, insecticides and fungicides [5]. Because of the highest electronegativity, high thermal stability and lipophilicity, fluorine endows various prominent functionalities in these compounds. Some examples demonstrate that the incorporation of fluorine atoms or fluorinated substituents into certain compounds influences the herbicidal activity [6], fungicidal activity [7] and insecticidal activity [8].

Recently, aza-Wittig reactions of functionalized iminophosphorane with isocyanates are used to produce carbodiimide, which lead to the preparation of quinazolines [9], imidazolinones [10] and pteridinones [11]. As part of our ongoing project aimed at investigating new bioactive heterocycles [12], we have designed a series of compounds which have the skeletons of thiazolo[4,5-*d*]pyrimidines. Herein, we would like to describe a facile synthesis of 6-aryl-5-(fluoro-substituted)alkyl-amino-3-phenyl-2-thioxo-2,3-dihydrothiaolo[4,5-*d*] pyrimidin-7-one derivatives **5** *via* the tandem aza-Wittig and cyclization reaction. The preliminary bioassay showed that some of them possess significant inhibition activities against the root growth of rape and barnyard grass.

2. Results and discussion

2.1. Synthesis

The iminophosphorane **2** [13], which was prepared by the reaction of 4-amino-2,3-dihydro-3-phenyl-2-thioxothiazole-5-carboxylate **1** [14] with triphenylphosphine and hexachloroethane using Et_3N as base in acetonitrile, was reacted with 1.1 equiv. of aryl isocyanate to afford carbodiimides **3**. The reaction of carbodiimides **3** with alkylamines at room temperature gave intermediate guanidines **4**. In the presence of EtONa/EtOH, the reaction proceeded smoothly at ambient temperature for 0.5–1 h to give **5** in good yields (Table 1). This process can be rationalized in Scheme 1.

---

* Corresponding author. Tel.: +86 27 67867960.
E-mail address: he1208@mail.ccnu.edu.cn (H.W. He).

0022-1139/$ – see front matter © 2007 Elsevier B.V. All rights reserved.
doi:10.1016/j.jfluchem.2007.04.011

Table 1
Yields of compounds **5**

Compounds	Ar	R	Yields
5a	Ph	*n*-Pr	82.6
5b	Ph	*n*-Bu	80.9
5c	Ph	*i*-Bu	79.3
5d	Ph	2-FPhCH$_2$	77.5
5e	Ph	3-FPhCH$_2$	80.4
5f	Ph	4-FPhCH$_2$	78.3
5g	4-FPh	*n*-Pr	82.4
5h	4-FPh	*n*-Bu	78.6
5i	4-FPh	*i*-Bu	71.6
5j	4-FPh	*t*-Bu	65.3
5k	4-FPh	2-MePhCH$_2$	77.2
5l	4-FPh	3-MePhCH$_2$	73.8
5m	4-FPh	4-MePhCH$_2$	76.5
5n	4-FPh	4-MeOPhCH$_2$	69.8
5o	4-FPh	4-ClPhCH$_2$	87.7
5p	4-FPh	2-FPhCH$_2$	76.4
5q	4-FPh	3-FPhCH$_2$	74.1
5r	4-FPh	4-FPhCH$_2$	74.9

In our previous research, we found that carbodiimides can react with nucleophiles easily in the presence of excessive solid potassium carbonate [12]. Herein we carried out the reactions of carbodiimides **3** with alkylamines using EtONa instead of potassium carbonate as catalyst. As a result, whether aliphatic or aromatic amines were used, the cyclization proceeded very smoothly and regioselectively.

All products of compounds **5** were obtained as yellow crystals after recrystallization from CH_2Cl_2/petroleum ether. The formation of compounds **5** (Scheme 2) could be rationalized in terms of geometry of the intermediates **4** and conjugative effect of compounds **5**. It was estimated that the configuration of carbodiimides **3** was almost coplanar due to the resonance effect. As the amines were reacted with **3**, intermediates **4a** were formed since the amines would attack **3** mainly from the opposite direction of CO_2Et group due to the steric hindrance of CO_2Et group. At the same time, compounds **4b** partly formed through C–N single-bond rotation. Compounds **4a** were suitable for the cyclization of arylamine group to obtain products **5**, and compounds **4b** were suitable for alkylamine group's cyclization to form products **6**. However, the compounds **5** are more stable than compounds **6** because of the conjugative effect between the thiazolopyrimidine ring and phenyl ring. Therefore, only compounds **5** were obtained regioselectively.

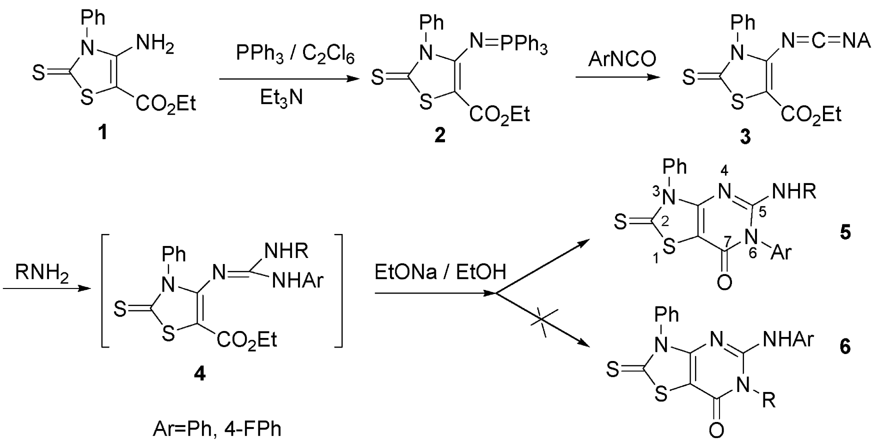
The structures of compounds **5** were fully confirmed by IR, ^{1}H NMR, MS and elementary analyses, and all structures were supported spectroscopically. For example, the ^{1}H NMR spectra of **5p** showed the signal of NH at δ 4.95 as triplet, which was not the same as the proton of PhNH, of which the chemical shift is greater than δ 7.0 [15]. And the methylene protons displayed a doublet also, which strongly suggested the existence of an $NHCH_2$-group. In IR spectra, the relatively strong absorption of N–H appeared at 3336–3431 cm^{-1}, which was only one peak. The stretching resonance of C–O showed strong absorption at about 1675–1697 cm^{-1}. The MS spectra displayed strong molecule ion peaks.

Compound **5p** was further identified by single-crystal X-ray diffraction (Fig. 1). In the crystal structure, the thiazolopyrimidine ring system is nearly coplanar, and the dihedral angles of this plane with phenyl and 4-F phenyl ring are 64.1° and 75.1°, respectively. The bond lengths of C(8)=C(9), C(11)=N(2) are 1.364(4), 1.315(3) Å, respectively, are longer than that of the typical C=C (1.34 Å) and C=N (1.28 Å), while the single bond lengths of C(8)–N(1), C(8)–N(2), C(10)–N(3), C(11)–N(3), C(9)–C(10), are 1.392(3), 1.349(3), 1.418(4), 1.383(3), 1.421(4) Å, respectively, which are significantly shorter than that of the typical C(sp2)–N (1.426 Å) and C–C (1.53 Å), showing a degree of delocalization.

2.2. Herbicidal activity

The herbicidal activity of all compounds **5** against *Brassica napus* (rape) and *Echinochloa crus-galli* (barnyard grass) has been investigated at the dosage of 100 and 10 mg/L using known procedure [16] compared with distilled water and 2,4-dichlorophenoxy acetic acid (2,4-D), a commercially available herbicide. The results of bioassay showed that

2.1 Synthesis



Scheme 1. Synthesis of the title compounds **5**.

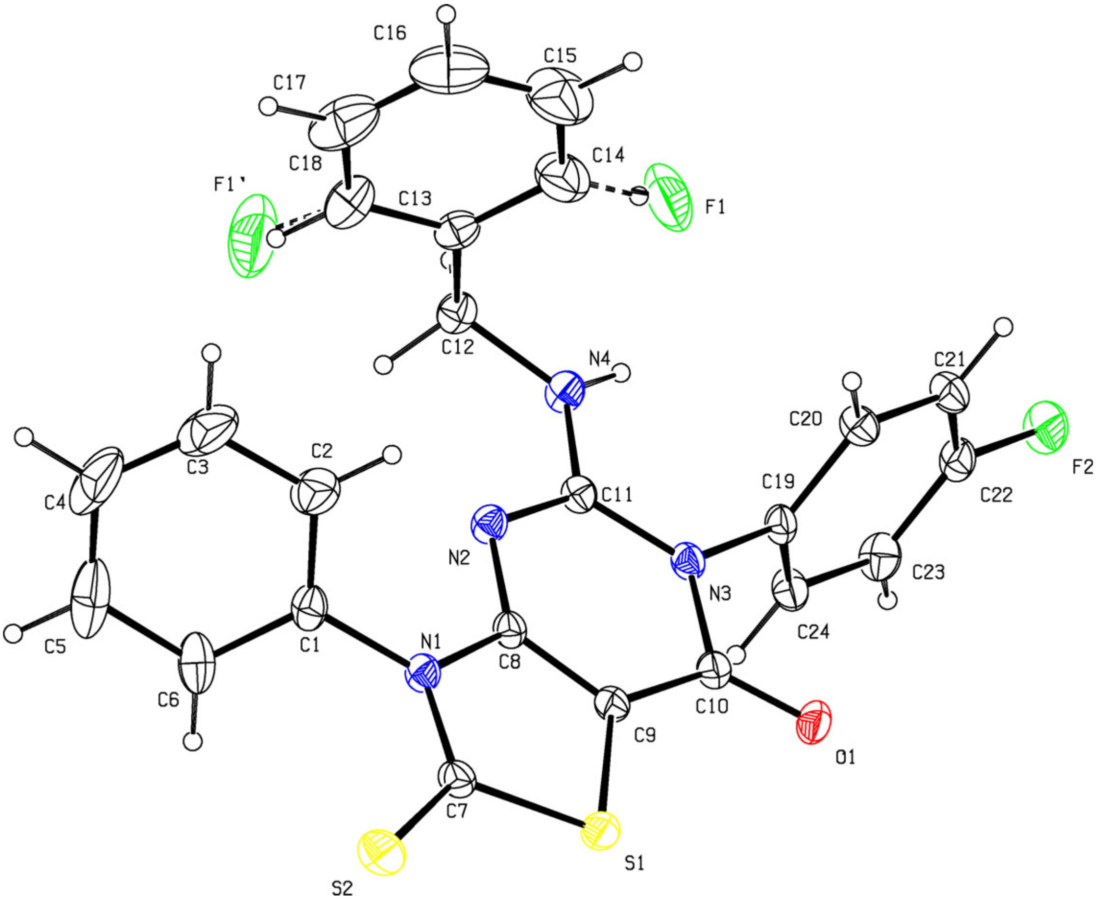
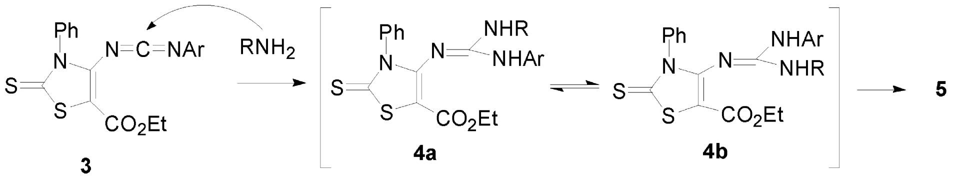


Fig. 1. View and atom labelling of **5p**.



Scheme 2. Formation of compounds **5**.

some of them exhibit significant herbicidal activity when fluorine atom is introduced (the inhibition rates are listed in Table 2).

As per the results listed in Table 2, fluorine-containing compounds **5d–f** and **5p–r** displayed much better herbicidal activities than other compounds. For example, **5d**, **5e**, **5q** showed high inhibition rate (>95%) against the root of rape and barnyard grass at the dosage of 100 mg/L. It showed that fluorine atom introduced to the 5 position of thiazolopyrimidine was useful for the improvement of inhibition activity, and the role of the fluorine position (*m*-, *p*-, *o*-) has no obvious influence on the inhibition activity. However, the introduction of fluorine atom to the 6 position of the thiazolopyrimidine was not helpful for the increase of the inhibition activity.

In conclusion, we developed a facile synthesis of the 5-alkylamino-6-aryl-3-phenyl-2-thioxo-2,3-dihydrothiazolo[4,5-*d*]pyrimidin-7(6H)-ones **5** by a novel regioselective cyclization process. The herbicidal activity of the title compounds could be improved to some extent by introducing fluorine moiety to the 5 position of the fused heterocycle system, and this scaffold may be further developed as lead compound.

3. Experimental

Melting points were measured on an electrothermal melting point apparatus and are uncorrected. **IR** spectra were recorded on a Nicolet Avatar360 FTIR spectrometer in KBr pellets. ^{1}H NMR spectra were performed on Mercury 400 (Varian, 400 MHz) spectrometer with $CDCl_3$ as solvent and TMS as internal standard. Mass spectra were determined on a Finnigan Trace MS 2000 spectrometer. Elemental analysis was taken on Elementar Vario EL III elementary analyzer. All the solvent and materials are reagent grades and purified before use.

Table 2
The herbicidal activity of compounds **5**

Compounds	Relative inhibition (root%/stalk%)			
	Rape		Barnyard grass	
	100 mg/L	10 mg/L	100 mg/L	10 mg/L
5a	59.6/36.7	22.8/3.3	67.6/3.8	48.6/17.3
5b	86.0/63.3	22.8/30.0	83.8/30.8	48.6/9.6
5c	84.2/63.3	24.6/6.7	75.7/19.2	40.5/25.0
5d	96.3/82.1	34.1/25.0	89.7/57.1	53.8/8.6
5e	98.8/89.3	39.0/28.6	94.9/77.1	48.7/20.0
5f	93.9/82.1	29.3/17.9	92.3/51.4	53.8/17.1
5g	78.0/30.3	48.6/27.3	40.0/31.6	21.4/15.8
5h	77.4/60.6	33.3/27.3	42.9/13.2	48.6/7.9
5i	47.3/33.3	22.6/24.2	31.4/13.2	20.0/−31.6
5j	24.7/15.2	23.7/3.0	20.0/15.8	14.3/15.8
5k	63.4/42.4	3.2/9.1	0/2.6	0/−18.4
5l	25.8/27.3	8.6/12.1	28.6/0	25.7/0
5m	72.3/29.1	29.4/12.1	51.4/12.6	−2.9/0
5n	70.1/39.4	29.7/13.0	65.7/18.4	22.9/10.5
5o	79.5/53.3	58.7/21.2	32.9/15.8	−20.0/21.1
5p	94.1/82.1	46.9/32.1	90.0/42.1	45.7/21.1
5q	96.7/83.3	63.7/42.1	87.0/48.4	31.4/15.8
5r	91.5/72.4	79.7/43.0	72.9/41.1	40.0/23.7
2,4-D	99.0/91.2	98.1/91.2	97.5/33.3	97.5/30.8

*3.1. Synthesis of 4-amino-2,3-dihydro-3-phenyl-2-thioxothiazole-5-carboxylate **1***

Intermediate **1** was synthesized according to the literature in 68.8% yield [13]. Yellow crystal, mp 221.8–222.4 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63–7.32 (m, 5H, Ph-H), 5.63 (s, 2H, $-NH_2$), 4.28 (q, 2H, $J = 7.2$ Hz, $-CH_2$), 0.97 (t, 3H, $J = 6.8$ Hz, $-CH_3$).

*3.2. Synthesis of iminophosphorane **2***

Imimophosphorane **2** was prepared according to the reported procedure in 98.5% yield [14]. Yellow crystal, mp 224.1–225.0 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50–7.27 (m, 20H, Ph-H), 3.75 (q, 2H, $J = 6.8$ Hz, $-CH_2$), 0.97 (t, 3H, $J = 7.2$ Hz, $-CH_3$); EI-MS (70 eV, *m/z*): 540 (M^+, 100), 512 (28), 262 (99), 183 (90), 107 (54).

*3.3. General procedure for the preparation of 5-alkylamino-6-aryl-3-phenyl-2-thioxo-2,3-dihydrothiazolo[4,5-d]pyrimidin-7(6H)-ones **5a–r***

Aryl isocyanate (2.2 mmol) was added to a solution of iminophosphorane **2** (2 mmol) in dry CH_2Cl_2 (15 mL) under an N_2 atmosphere at room temperature. After the reaction mixture was allowed to stand for 5–12 h, the solvent was removed under reduced pressure. To the residue, Et_2O and petroleum ether (1:1, v/v) were added, and the side product triphenyl phosphine oxide was precipitated and removed subsequently by filtration. The solvent was removed to give the corresponding carbodiimide **3**, which was used directly without further purification. Alkylamine (2.2 mmol) and a catalytic amount of sodium ethoxide in ethanol were added to a solution of the carbodiimide **3** in ethanol (15 mL). After the mixture had been stirred for 0.5–1 h at 303 K, the solution was concentrated and the residue was recrystallized from CH_2Cl_2/petroleum ether to give pure 5-alkylamino-6-aryl-3-phenyl-2-thioxo-2,3-dihydrothiazolo[4,5-*d*]pyrimidin-7(6H)-ones **5a–r** [17].

*3.3.1. 3,6-Diphenyl-5-(n-propylamino)-2-thioxo-2,3-dihydrothiazolo[4,5-d] pyrimidin-7(6H)-one (**5a**)*

Yellow crystal, yield 82.6%, mp 230.6–231.2 °C; IR (KBr) υ 3347, 2955, 1689, 1549 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.67 (t, 3H, $J = 7.2$ Hz, CH_3), 1.34 (q, 2H, $J = 7.2$ Hz, CH_2), 3.01 (q, 2H, $J = 6.8$ Hz, $NHCH_2$), 4.40 (s, 1H, NH), 7.27–7.63 (m, 10H, Ph-H); EI-MS (70 eV, *m/z*): 394 (M^+, 100), 351 (73), 336 (6), 118 (20), 103 (8), 77 (24); Elemental Anal. Calcd. for $C_{20}H_{18}N_4OS_2$: C, 60.89; H, 4.60; N, 14.20; S, 16.26. Found: C, 61.06; H, 4.78; N, 14.03; S, 16.58.

*3.3.2. 3,6-Diphenyl-5-(n-butylamino)-2-thioxo-2,3-dihydrothiazolo[4,5-d] pyrimidin-7(6H)-one (**5b**)*

Yellow crystal, yield 80.9%, mp 233.1–234.6 °C; IR (KBr): υ 3352, 2952, 1684, 1551 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.74 (t, 3H, $J = 7.2$ Hz, CH_3), 1.02–1.11 (m, 2H, CH_2), 1.26–1.31 (m, 2H, CH_2), 3.04 (q, 2H, $J = 7.2$ Hz, CH_2), 4.37 (s, 1H, NH), 7.25–7.64 (m, 10H, Ph-H); EI-MS (70 eV, *m/z*): 408 (M^+, 100), 351 (76), 336 (9), 119 (13), 103 (7), 77 (31); Elemental Anal. Calcd. for $C_{21}H_{20}N_4OS_2$: C, 61.74; H, 4.93; N, 13.71; S, 15.70. Found: C, 61.36; H, 5.24; N, 13.78; S, 15.89.

*3.3.3. 3,6-Diphenyl-5-(iso-butylamino)-2-thioxo-2,3-dihydrothiazolo[4,5-d] pyrimidin-7(6H)-one (**5c**)*

Yellow crystal, yield 79.3%, mp 235.7–236.8 °C; IR (KBr): υ 3364, 2958, 1681, 1548 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.66 (d, 6H, $J = 6.4$ Hz, $2CH_3$), 1.62–1.65 (m, 1H, CH), 2.85 (t, 2H, $J = 6.4$ Hz, CH_2), 4.45 (s, 1H, NH), 7.27–7.65 (m, 10H, Ph-H); EI-MS (70 eV, *m/z*): 408 (M^+, 100), 351 (64), 336 (14), 262 (19), 119 (21), 103 (15), 77 (36); Elemental Anal. Calcd. for $C_{21}H_{20}N_4OS_2$: C, 61.74; H, 4.93; N, 13.71; S, 15.70. Found: C, 62.15; H, 4.99; N, 13.48; S, 15.14.

*3.3.4. 3,6-Diphenyl-5-(2-fluorobenzylamino)-2-thioxo-2,3-dihydrothiazolo[4,5-d] pyrimidin-7(6H)-one (**5d**)*

Yellow crystal, yield 77.5%, mp 245.2–246.6 °C; IR (KBr): υ 3384, 2941, 1676, 1544 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.19 (d, 2H, $J = 6.0$ Hz, CH_2), 4.99 (s, 1H, NH), 6.52–7.66 (m, 14H, Ph-H); Elemental Anal. Calcd. for $C_{24}H_{17}FN_4OS_2$: C, 62.59; H, 3.72; N, 12.17; S, 13.92. Found: C, 62.79; H, 3.61; N, 12.42; S, 13.76.

*3.3.5. 3,6-Diphenyl-5-(3-fluorobenzylamino)-2-thioxo-2,3-dihydrothiazolo[4,5-d] pyrimidin-7(6H)-one (**5e**)*

Yellow crystal, yield 80.4%, mp 258.4–259.7 °C; IR (KBr) υ 3372, 2962, 1683, 1543 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.15 (d, 2H, $J = 6.0$ Hz, CH_2), 4.90 (s, 1H, NH), 6.54–7.65 (m, 14H, Ph-H); Elemental Anal. Calcd. for $C_{24}H_{17}FN_4OS_2$: C, 62.59; H, 3.72; N, 12.17; S, 13.92. Found: C, 62.75; H, 3.83; N, 12.09; S, 14.12.

*3.3.6. 3,6-Diphenyl-5-(4-fluorobenzylamino)-2-thioxo-2,3-dihydrothiazolo[4,5-d] pyrimidin-7(6H)-one (**5f**)*

Yellow crystal, yield 78.3%, mp 260.4–261.2 °C; IR (KBr) υ 3399, 2954, 1676, 1546 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 4.11 (d, 2H, $J = 6.0$ Hz, CH$_2$), 4.89 (s, 1H, NH), 6.75–7.64 (m, 14H, Ph-H); EI-MS (70 eV, *m/z*): 460 (M^+, 38), 351 (12), 185 (25), 109 (100), 103 (24), 91 (21), 77 (50); Elemental Anal. Calcd. for $C_{24}H_{17}FN_4OS_2$: C, 62.59; H, 3.72; N, 12.17; S, 13.92. Found: C, 62.26; H, 3.54; N, 12.29; S, 14.21.

*3.3.7. 6-(4-Fluorophenyl)-5-(n-propylamino)-3-phenyl-2-thioxo-2,3-dihydrothiazolo [4,5-d]pyrimidin-7(6H)-one (**5g**)*

Yellow crystal, yield 82.4%, mp 231.1–232.7 °C; IR (KBr): υ 3336, 2955, 1682, 1597, 1551 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 0.68 (t, 3H, $J = 7.2$ Hz, CH$_3$), 1.34 (q, 2H, $J = 7.2$ Hz, CH$_2$), 3.01 (q, 2H, $J = 6.8$ Hz, NHCH$_2$), 4.37 (s, 1H, NH), 7.28–7.58 (m, 9H, Ph-H); EI-MS (70 eV, *m/z*): 412 (M^+, 100), 369 (96), 275 (11), 136 (71), 95 (46), 77 (64); Elemental Anal. Calcd. for $C_{20}H_{17}FN_4OS_2$: C, 58.23; H, 4.15; N, 13.58; S, 15.55. Found: C, 58.59; H, 4.26; N, 13.47; S, 15.48.

*3.3.8. 6-(4-Fluorophenyl)-5-(n-butylamino)-3-phenyl-2-thioxo-2,3-dihydrothiazolo[4,5-d] pyrimidin-7(6H)-one (**5h**)*

Yellow crystal, yield 78.6%, mp 250.6–252.1 °C; IR (KBr): υ 3347, 2951, 1682, 1552 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 0.74 (t, 3H, $J = 7.2$ Hz, CH$_3$), 1.02–1.17 (m, 2H, CH$_2$), 1.26–1.34 (m, 2H, CH$_2$), 3.04 (q, 2H, $J = 6.8$ Hz, NHCH$_2$), 4.37 (s, 1H, NH), 7.27–7.58 (m, 9H, Ph-H); EI-MS (70 eV, *m/z*): 426 (M^+, 100), 369 (92), 275 (9), 136 (67), 109 (43), 95 (42), 77 (59); Elemental Anal. Calcd. for $C_{21}H_{19}FN_4OS_2$: C, 59.13; H, 4.49; N, 13.14; S, 15.04. Found: C, 59.58; H, 4.76; N, 13.26; S, 14.94.

*3.3.9. 6-(4-Fluorophenyl)-5-(iso-butylamino)-3-phenyl-2-thioxo-2,3-dihydrothiazolo [4,5-d]pyrimidin-7(6H)-one (**5i**)*

Yellow crystal, yield 71.6%, mp 256.2–257.4 °C; IR (KBr): υ 3339, 2959, 1678, 1576, 1547 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 0.67 (d, 6H, $J = 6.8$ Hz, 2CH$_3$), 1.63–1.66 (m, 1H, CH), 2.87 (t, 2H, $J = 6.4$ Hz, CH$_2$), 4.42 (s, 1H, NH), 7.27–7.58 (m, 9H, Ph-H); EI-MS (70 eV, *m/z*): 426 (M^+, 75), 369 (100), 275 (4), 136 (29), 109 (15), 95 (21), 77 (26); Elemental Anal. Calcd. for $C_{21}H_{19}FN_4OS_2$: C, 59.13; H, 4.49; N, 13.14; S, 15.04. Found: C, 59.13; H, 4.49; N, 13.14; S, 15.04.

*3.3.10. 6-(4-Fluorophenyl)- 3-phenyl-5-(tert-butylamino)-2-thioxo-2,3-dihydrothiazolo [4,5-d]pyrimidin-7(6H)-one (**5j**)*

Yellow crystal, yield 69.6%, mp 225.4–227.1 °C; IR (KBr): υ 3431, 2969, 1685, 1580, 1548 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.05 (s, 9H, 3CH$_3$), 4.15 (s, 1H, NH), 7.27–7.58 (m, 9H, Ph-H); EI-MS (70 eV, *m/z*): 426 (M^+, 68), 369 (100), 277 (6), 136 (27), 109 (13), 95 (27), 77 (30); Elemental Anal. Calcd. for $C_{21}H_{19}FN_4OS_2$: C, 59.13; H, 4.49; N, 13.14; S, 15.04. Found: C, 59.59; H, 4.67; N, 13.01; S, 14.68.

*3.3.11. 6-(4-Fluorophenyl)-5-(2-methylbenzylamino)-3-phenyl-2-thioxo-2,3-dihydrothiazolo[4,5-d]pyrimidin-7(6H)-one (**5k**)*

Yellow crystal, yield 77.2%, mp 255.3–256.8 °C; IR (KBr): υ 3376, 2956, 1673, 1542 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.99 (s, 3H, CH$_3$), 4.20 (d, 2H, $J = 5.6$ Hz, CH$_2$), 4.69 (s, 1H, NH), 6.70–7.59 (m, 13H, Ph-H); Elemental Anal. Calcd. for $C_{25}H_{19}FN_4OS_2$: C, 63.27; H, 4.04; N, 11.81; S, 13.51. Found: C, 63.58; H, 4.09; N, 11.56; S, 13.59.

*3.3.12. 6-(4-Fluorophenyl)-5-(3-methylbenzylamino)-3-phenyl-2-thioxo-2,3-dihydrothiazolo[4,5-d]pyrimidin-7(6H)-one (**5l**)*

Yellow crystal, yield 73.8%, mp 261.2–263.1 °C; IR (KBr): υ 3366, 2933, 1675, 1543 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 2.27 (s, 3H, CH$_3$), 4.16 (d, 2H, $J = 6.0$ Hz, CH$_2$), 4.79 (s, 1H, NH), 6.65–7.60 (m, 13H, Ph-H); EI-MS (70 eV, *m/z*): 474 (M^+, 94), 367 (15), 199 (56), 136 (20), 105 (100), 95 (17), 77 (75); Elemental Anal. Calcd. for $C_{25}H_{19}FN_4OS_2$: C, 63.27; H, 4.04; N, 11.81; S, 13.51. Found: C, 63.54; H, 3.79; N, 11.49; S, 13.67.

*3.3.13. 6-(4-Fluorophenyl)-5-(4-methylbenzylamino)-3-phenyl-2-thioxo-2,3-dihydrothiazolo[4,5-d]pyrimidin-7(6H)-one (**5m**)*

Yellow crystal, yield 76.5%, mp 255.7–257.1 °C; IR (KBr): υ 335, 2940, 1680, 1546 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 2.30 (s, 3H, CH$_3$), 4.13 (d, 2H, $J = 5.6$ Hz, CH$_2$), 4.80 (s, 1H, NH), 6.74–7.62 (m, 13H, Ph-H); EI-MS (70 eV, *m/z*): 474 (M^+, 100), 369 (35), 199 (60), 136 (27), 109 (20), 95 (21), 77 (60); Elemental Anal. Calcd. for $C_{25}H_{19}FN_4OS_2$: C, 63.27; H, 4.04; N, 11.81; S, 13.51. Found: C, 63.55; H, 4.37; N, 11.94; S, 13.45.

*3.3.14. 6-(4-Fluorophenyl)-5-(4-methoxybenzylamino)-3-phenyl-2-thioxo-2,3-dihydrothiazolo[4,5-d]pyrimidin-7(6H)-one (**5n**)*

Yellow crystal, yield 69.8%, mp 230.7–231.6 °C; IR (KBr): υ 3316, 2939, 1678, 1545 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 3.77 (s, 3H, CH$_3$), 4.11 (d, 2H, $J = 6.0$ Hz, CH$_2$), 4.78 (s, 1H, NH), 6.70–7.63 (m, 13H, Ph-H); EI-MS (70 eV, *m/z*): 490 (M^+, 100), 121 (50), 77 (8); Elemental Anal. Calcd. for $C_{25}H_{19}FN_4O_2S_2$: C, 61.21; H, 3.90; N, 11.42; S, 13.07. Found: C, 61.43; H, 4.16; N, 11.20; S, 13.21.

*3.3.15. 5-(4-Chlorobenzylamino)-6-(4-fluorophenyl)-3-phenyl-2-thioxo-2,3-dihydrothiazolo[4,5-d]pyrimidin-7(6H)-one (**5o**)*

Yellow crystal, yield 87.7%, mp 248.2–249.6 °C; IR (KBr): υ 3295, 2943, 1681, 1543 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 4.12 (d, 2H, $J = 6.0$ Hz, CH$_2$), 4.88 (s, 1H, NH), 6.73–7.63 (m, 13H, Ph-H); EI-MS (70 eV, *m/z*): 494 (M^+, 18), 219 (40), 191 (11), 136 (27), 109 (10), 77 (15); Elemental Anal. Calcd. for $C_{24}H_{16}ClFN_4OS_2$: C, 58.23; H, 3.26; N, 11.32; S, 12.93. Found: C, 58.27; H, 3.35; N, 11.37; S, 12.98.

3.3.16. 5-(2-Fluorobenzylamino)-6-(4-fluorophenyl)-3-phenyl-2-thioxo-2,3-dihydrothiazolo[4,5-d]pyrimidin-7(6H)-one (5p)

Yellow crystal, yield 76.4%, mp 268.2–269.5 °C; IR (KBr): υ 3378, 2936, 1675, 1546 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.20 (d, 2H, J = 6.0 Hz, CH_2), 4.95 (s, 1H, NH), 6.50–7.66 (m, 13H, Ph-H); EI-MS (70 eV, *m/z*): 478 (M^+, 100), 202 (43), 135 (19), 108 (82), 77 (24); Elemental Anal. Calcd. for $C_{24}H_{16}F_2N_4OS_2$: C, 60.24; H, 3.37; N, 11.71; S, 13.40. Found: C, 60.48; H, 3.19; N, 12.23; S, 13.87.

3.3.17. 5-(3-Fluorobenzylamino)-6-(4-fluorophenyl)-3-phenyl-2-thioxo-2,3-dihydrothiazolo[4,5-d]pyrimidin-7(6H)-one (5q)

Yellow crystal, yield 74.1%, mp 266.6–267.8 °C; IR (KBr): υ 3359, 2940, 1679, 1545 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.16 (d, 2H, J = 5.6 Hz, CH_2), 4.87 (d, 1H, J = 5.6 Hz, NH), 6.55–7.60 (m, 13H, Ph-H); EI-MS (70 eV, *m/z*): 478 (M^+, 14), 369 (4), 203 (11), 109 (100), 95 (14), 77 (36); Elemental Anal. Calcd. for $C_{24}H_{16}F_2N_4OS_2$: C, 60.24; H, 3.37; N, 11.71; S, 13.40. Found: C, 60.59; H, 3.50; N, 11.80; S, 13.55.

3.3.18. 5-(4-Fluorobenzylamino)-6-(4-Fluorophenyl)-3-phenyl-2-thioxo-2,3-dihydrothiazolo[4,5-d]pyrimidin-7(6H)-one (5r)

Yellow crystal, yield 74.9%, mp 272.4–273.6 °C; IR (KBr): υ 3332, 2954, 1676, 1545 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.13 (d, 2H, J = 5.6 Hz, CH_2), 4.85 (s, 1H, NH), 6.76–7.63 (m, 13H, Ph-H); EI-MS (70 eV, *m/z*): 478 (M^+, 44), 367 (11), 203 (52), 109 (100), 95 (22), 77 (43); Elemental Anal. Calcd. for $C_{24}H_{16}F_2N_4OS_2$: C, 60.24; H, 3.37; N, 11.71; S, 13.40. Found: C, 60.49; H, 3.41; N, 11.98; S, 13.25.

3.4. Herbicidal testing

Herbicidal testing of the newly synthesized compounds **5** was carried out in a plant growth room; temperature 23 ± 1 °C, RH 60 ± 5%, light intensity 10 klx and photoperiod 8 h/day. Twenty seeds of each species including rape and barnyard grass were chosen for testing. Seedlings were grown in the test plates of 9 cm diameter containing two pieces of filter paper and 9 mL solution of the tested compound (100 and 10 mg/L, respectively). Distilled water and 2,4-dichlorophenoxyl acetic acid (2,4-D), a commercially available herbicide in the market, were used as comparison compound. The herbicidal activity was assessed as the inhibition rate in comparison with the distilled water. The herbicidal rating score was based on visual observation; range from 0% to 100%: 0% means no effect, 100% means complete killing.

3.5. Crystal structure determination

Single-crystal X-ray diffraction data for **5p** at 292 K on a Bruker Smart Apex Area CCD equipped with Mo Kα radiation (λ = 0.71073 Å). Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication No. CCDC-632746. Copies of the data can be obtained, free of charge, on application to CCDC, Cambridge, UK (fax: +44 1223 336033 or email: deposit@ccdc.cam.ac.uk).

Acknowledgment

We gratefully acknowledge financial support of this work by National Key Basic Research Development Program of China (No. 2003CB114400) and National Natural Science Foundation of China (Nos. 20072008 and 20372023).

References

[1] (a) N.S. Habin, S.M. Rida, E.A.M. Badaway, H.T.Y. Fahwy, Monatsh. Chem. 127 (1996) 1203–1207;
(b) H.T.Y. Fahmy, S.A.F. Rostom, M.N. Saudi, J.K. Zjawiony, Arch. Pharm. Pharm. Med. Chem. 336 (2003) 216–225;
(c) A.A. Bekhit, H.T.Y. Fahmy, S.A.F. Rostom, A.M. Baraka, Eur. J. Med. Chem. 38 (2003) 27–32.
[2] (a) K. Danel, E.B. Pedersen, C. Nielsen, J. Med. Chem. 41 (1998) 191–198;
(b) G.D. Kini, J.D. Anderson, Y.S. Sanghvi, A.F. Lewis, D.F. Smee, G.R. Revankar, R.K. Robins, H.B. Cottam, J. Med. Chem. 34 (1991) 3006–3010;
(c) B. Tozkoparan, M. Ertan, P. Kelicen, R. Demirdamar, Il Farmaco 54 (1999) 588–593.
[3] (a) M. Hellberg, J.F. Stubbins, R.A. Glennon, Bioorg. J. Med. Chem. 8 (2000) 1917–1923;
(b) A. Balkan, H. Urgan, M. Ozalp, Arzneim-Forsch. 51 (2001) 839–842.
[4] N.S. Habin, S.M. Rida, E.A.M. Badaway, H.T.Y. Fahwy, H.A. Ghozlan, Eur. J. Med. Chem. 32 (1997) 759–762.
[5] P. Jeschke, ChemBioChem. 5 (2004) 570.
[6] Y.X. Liu, Q.Q. Zhao, Q.M. Wang, H. Li, R.Q. Huang, Y.H. Li, J. Fluorine Chem. 126 (2005) 345–348.
[7] X.Y. Xua, X.H. Qian, Z. Lia, G.H. Song, W.D. Chen, J. Fluorine Chem. 126 (2005) 297–300.
[8] X.M. Zheng, Z. Li, Y.L. Wang, W.D. Chen, Q.C. Huang, C.X. Liu, G.H. Song, J. Fluorine Chem. 123 (2003) 163–169.
[9] M.W. Ding, G.P. Zeng, T.J. Wu, Synth. Commun. 30 (2000) 1599–1604.
[10] M.W. Ding, Z.F. Xu, T.J. Wu, Synth. Commun. 29 (1999) 1171–1176.
[11] T. Okawa, S. Eguchi, A. Kakehi, J. Chem. Soc., Perkin Trans I (1996) 247–254.
[12] (a) J.C. Liu, H.W. He, Q.Y. Ren, M.W. Ding, J. Heterocycl. Chem. 43 (2006) 803–806;
(b) J.C. Liu, H.W. He, Q.Y. Ren, M.W. Ding, Helv. Chim. Acta 89 (2006) 1337–1343.
[13] H. Wamhoff, S. Herrmann, S. Stolben, Tetrahedron 49 (1993) 581–583.
[14] M.A.F. Sharaf, F.A. Abdel, A.M. Abdel, A.M.R. Abdel, J. Chem. Res. Synop. 8 (1996) 354–356.
[15] E.C. Taylor, M. Patel, J. Heterocyclic. Chem. 28 (1991) 1857–1861.
[16] T. Chen, P. Shen, Y.J. Li, H.W. He, J. Fluorine Chem. 127 (2006) 291–295.
[17] Y. Liang, H.W. He, Acta Crystallogr. Section E 63 (2007) o252–o253.