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Novel 2*H*-[1,2,4]thiadiazolo[2,3-*a*]pyrimidine derivatives bearing chiral *S*(−)-2-(4-chlorophenyl)-3-methylbutyric acid moiety: Design, synthesis and herbicidal activity

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KEYWORDS

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Chirality;
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Abstract A series of *S*(−)-2-(4-chlorophenyl)-*N*-(5,7-disubstituted-2*H*-[1,2,4]-thiadiazolo[2,3-*a*]pyrimidin-2-ylidene)-3-methylbutanamide derivatives were designed and synthesized. The structures of all the newly synthesized compounds had been identified by elemental analysis, ^{1}H NMR, MS and optical rotation. Their herbicidal activities were evaluated against a variety of weeds. The preliminary results showed that most of the target compounds had moderate inhibitory activities and selectivities against root and stalk of monocotyledon and dicotyledon plants. More importantly, the chiral target compounds showed improved herbicidal activities to some extent over their racemic counterparts against a variety of tested weeds, which might be contributed by the introduction of chiral active unit. The present work provided a novel class of chirality-based thiadiazolopyrimidine derivatives with potent herbicidal activities for further optimization.

1. Introduction

Many of agrochemicals currently in use were chiral, and these were increasing as more structurally complicated compounds were introduced into use (Williams, 1996; Cai et al., 2008; Spangler et al., 1999; Lao and Gan, 2006). It was noteworthy that stereochemistry strongly influenced not only biological activity but also metabolic processes in organisms and in the environment (Zhu et al., 2007). Growing concern about the side effects of chiral agrochemicals had promoted the use of enantiomerically pure or stereochemically enriched compounds (Williams, 1996). Therefore, a great of work have been performed on this important research topic during the recent years (Hosokawa et al., 2001; Song et al., 2005; Tanaka et al., 2002; Omokawa et al., 2003; Zhou et al., 2007; Rügge et al., 2002).

In our research group, we have been interested in studying the design, synthesis, and biological activity of compounds containing the 2*H*-[1,2,4]thiadiazolo[2,3-*a*]pyrimidine (Xue et al.,2004a,b, 2005a,b). 2*H*-[1,2,4]thiadiazolo[2,3-*a*]pyrimidine derivatives were an important class of synthetic herbicide (Xue

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et al., 1998; Zhang and Xue, 1995), which were active against the weeds of *Digitaria sanguinalis* (L) Scop and Chenopodium. Generally, this kind of compounds behaved in a manner similar to that of sulfonylurea herbicides, inhibiting the synthesis of acetolactate, which has become a very attractive target for herbicides (Schloss et al., 1988; Abell et al., 1995). It was well known that *S*(−)-2-(4-chlorophenyl)-3-methylbutyric acid was proved to have excellent biological activities over its non-active counterpart, such as antibacterial, pesticidal properties and promoting effect on plant growth (Elliott et al., 1974; Crammer et al., 1985). These inspired us to assume that 2*H*-[1,2,4]thiadiazolo[2,3-*a*]pyrimidine derivatives incorporated with enantiomerically active *S*(−)-2-(4-chlorophenyl)-3-methylbutyric acid might have some improved or different biological activities. Based on this consideration, a series of *S*(−)-2-(4-chlorophenyl)-*N*-(5,7-disubstituted-2*H*-[1,2,4]-thiadiazolo[2,3-*a*]pyrimidin-2-ylidene)-3-methylbutanamide derivatives were designed and synthesized, and their herbicidal activities were evaluated against a variety of weeds. The preliminary results showed that the target compounds showed improved herbicidal activities over their racemic counterpart against root and stalk of monocotyledon and dicotyledon plants.

2. Experimental

2.1. Material and reagents

All the reagents and solvents were of the commercial quality and were used without purification. Elemental analysis was performed on a PE-2400 elemental analyze, the C, H and N analysis were repeated twice. ^{1}H NMR spectra were obtained with a Bruker AM-400 spectrometer with chemical shifts reported as ppm (in DMSO-d_6, TMS as internal standard). Mass spectra were recorded on a HP-5988A mass spectrometer at 70 ev. Melting points were determined by an X-6 micro-melting point apparatus and were uncorrected.

2.2. General procedure for the preparation of 2H-[1,2,4]thiadiazolo[2,3-a]pyrimidine derivatives (5a–f)

The synthetic routes of the target compounds **5a**–**f** were shown in Scheme 1. According to our reported procedure (Xue et al., 2004a,b), *S*(−)-2-(4-chlorophenyl)-3-methylbutyric acid **1**, prepared by using the previously reported method (Zhang and Zhao, 2008), were treated with $SOCl_2$ and KSCN, respectively, affording the intermediates **2** with moderate yields of 75%, which were used directly without further purification. The following nucleophilic reaction of **2** with 4,6-disubstituted-2-amino-pyrimidine **3a**–**f**, led to the key intermediates **4a**–**f**, respectively. The subsequent oxidizing cyclization of **4a**–**f** with Br_2 in CH_2Cl_2 afforded the target compounds **5a**–**f**, which were recrystallized twice from DMF/EtOH/H_2O with satisfied yields of 75–80%, respectively.

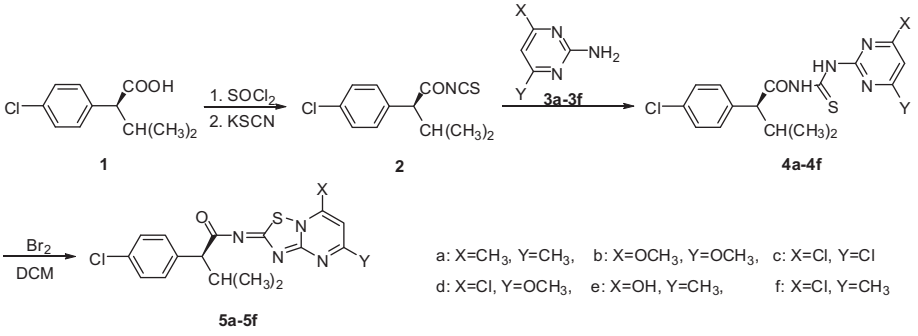
All the target compounds were pale yellow solid and stable at room temperature, no hygroscopic, insoluble in water and readily soluble in DMF and DMSO.

5a: *S*(−)-2-(4-chlorophenyl)-*N*-(5,7-dimethyl-2*H*-[1,2,4]thiadiazolo[2,3-*a*]pyrimidin-2-ylidene)-3-methyl butanamide. Yield 78%, mp 254–256 °C. $[\alpha]_D^{20}$, −10.5 (*c*, 1.15, methanol). ^{1}H NMR δ ppm: 0.70 (3H,d, CH(*CH*$_3$)$_2$), 0.90 (3H, d, CH(*CH*$_3$)$_2$), 2.20–2.40 (1H, m, *CH*(CH$_3$)$_2$), 2.10 (3H, s, CH$_3$), 2.20 (3H, s, CH$_3$), 3.90–4.10 (1H, m, *CH*CH(CH$_3$)$_2$), 5.94 (1H, s, py-5′-H), 7.30-7.50 (4H, m, Ph-H). MS (EI$^+$) calcd for $C_{18}H_{19}ClN_4OS$ M$^+$ 374.1, found 374.5. Element *Anal*. Calc. for $C_{18}H_{19}ClN_4OS$ M$^+$ 374.1: C 57.67, H 5.11, N 14.94. Found: C 57.61, H 5.15, N 14.92%.

5b: *S*(−)-2-(4-chlorophenyl)-*N*-(5,7-dimethoxy-2*H*-[1,2,4]thiadiazolo[2,3-*a*]pyrimidin-2-ylidene)-3-methyl butanamide. Yield 80%, mp 252–255 °C. $[\alpha]_D^{20}$, −19.2 (*c*, 0.90, methanol). ^{1}H NMR δ ppm: 0.80 (3H, d, CH(*CH*$_3$)$_2$), 1.00 (3H, d, CH(*CH*$_3$)$_2$), 2.10–2.30 (1H, m, *CH*(CH$_3$)$_2$), 3.80–4.00 (1H, m, *CH*CH(CH$_3$)$_2$), 4.41 (3H, s, CH$_3$), 4.60 (3H, s, CH$_3$), 5.91 (1H, s, py-5′-H), 7.20–7.40 (4H, m, Ph-H). MS (EI$^+$) calcd for $C_{18}H_{19}ClN_4O_3S$. M$^+$ 406.1, found 406.3. Element *Anal*. Calc. for $C_{18}H_{19}ClN_4O_3S$: C 53.13, H 4.71, N 13.77. Found: C 53.10, H 4.76, N 13.72%.

5c: *S*(−)-2-(4-chlorophenyl)-*N*-(5,7-dichloro-2*H*-[1,2,4]thiadiazolo[2,3-*a*]pyrimidin-2-ylidene)-3-methyl-butanamide. Yield 76%, mp 245–247 °C. $[\alpha]_D^{20}$, −19.0 (*c*, 1.00, methanol). ^{1}H NMR δ ppm: 1.00 (3H, d, CH(*CH*$_3$)$_2$), 1.20 (3H, d, CH(*CH*$_3$)$_2$), 2.45–2.55 (1H, m, *CH*(CH$_3$)$_2$), 3.90–4.00 (1H, m, *CH*CH(CH$_3$)$_2$), 6.92 (1H, s, py-5′-H), 7.30–7.40 (4H, m, Ph-H). MS (EI$^+$) calcd for $C_{16}H_{13}Cl_3N_4OS$ M$^+$ 415.7, found 416.0. Element *Anal*. Calc. for $C_{16}H_{13}Cl_3N_4OS$: C 46.23, H 3.15, N 13.48. Found: C 46.29, H 3.08, N 13.40%.

5d: *S*(−)-*N*-(7-chloro-5-methoxy-2*H*-[1,2,4]thiadiazolo[2,3-*a*]pyrimidin-2-ylidene)-2-(4-chlorophenyl)-3-methylbutanamide. Yield 75%, mp 251–253 °C. $[\alpha]_D^{20}$, −10.9 (*c*, 1.80, methanol). ^{1}H NMR δ ppm: 1.00 (3H, d, CH(*CH*$_3$)$_2$), 1.10 (3H, d, CH(*CH*$_3$)$_2$), 2.30–2.40 (1H, m, *CH*(CH$_3$)$_2$), 3.90–4.00 (1H, m, *CH*CH(CH$_3$)$_2$), 4.15 (3H, s, OCH$_3$), 5.74 (1H, s, py-5′-H), 7.50–7.60 (4H, m, Ph-H). MS (EI$^+$) calcd for $C_{17}H_{16}Cl_2N_4O_2S$ M$^+$ 410.0, found 410.2. Element *Anal*. Calc. for $C_{17}H_{16}Cl_2$-



Scheme 1 The synthetic routes of the target compounds.

N_4O_2S: C 49.64, H 3.92, N 13.62. Found: C 49.72, H 3.85, N 13.59%.

5e: *S*(−)-2-(4-chlorophenyl)-*N*-(5-hydroxy-7-methyl-2*H*-[1,2,4]thiadiazolo[2,3-*a*]pyrimidin-2-ylidene)-3-methylbutanamide. Yield 80%, mp >300 °C. $[\alpha]_D^{20}$, −12.1 (*c*, 0.50, methanol). ^{1}H NMR δ ppm: 0.90 (3H, d, $CH(CH_3)_2$), 1.10 (3H, d, $CH(CH_3)_2$), 2.40-2.55 (1H, m, $CH(CH_3)_2$), 2.49 (3H, s, CH_3), 3.90–4.05 (1H,m, $CHCH(CH_3)_2$), 6.87 (1H, s, py-5′-H), 7.30–7.50 (4H, m, Ph-H). MS (EI^+) calcd for $C_{17}H_{17}ClN_4O_2S$ M^+ 376.1, found 376.1. Element *Anal*. Calc. for $C_{17}H_{17}ClN_4O_2S$: C 54.18, H 4.55, N 14.87. Found: C 54.24, H 4.51, N 14.82%.

5f: *S*(−)-*N*-(7-chloro-5-methyl-2*H*-[1,2,4]thiadiazolo[2,3-*a*]pyrimidin-2-ylidene)-2-(4-chlorophenyl)-3-methylbutanamide. Yield 80%, mp 235–237 °C. $[\alpha]_D^{20}$, −14.3 (*c*, 0.80, methanol). ^{1}H NMR δ ppm: 1.00 (3H, d, $CH(CH_3)_2$), 1.10 (3H, d, $CH(CH_3)_2$), 2.11 (3H, s, CH_3), 2.30–2.40 (1H, m, $CH(CH_3)_2$), 3.90–4.00 (1H, m, $CHCH(CH_3)_2$), 5.74 (1H, s, py-5′-H), 7.50–7.60 (4H, m, Ph-H). MS (EI^+) calcd for $C_{17}H_{16}Cl_2N_4OS$ M^+ 394.0, found 394.2. Element *Anal*. Calc. for $C_{17}H_{16}Cl_2N_4OS$: C 51.65, H 4.08, N 14.17. Found: C 51.72, H 3.99, N 14.10%.

2.3. Biological activity

The herbicidal activities of target compounds were evaluated by flat-utensil method according with the standard bioactivity test procedures of Shanghai Academy of Agricultural Sciences in China (Xue et al., 2005a,b). The three monocotyledon weeds and two dicotyledon weeds used to test the herbicidal activity of compounds are *Echinochloa crusgallis* L., *Sorghum bicolort, Digitaria sanguinalis (L.) scop Chenopodium serotinum (L.) and Amaranthus retroflexus* L., respectively. Seeds were planted in a 6 cm-diameter flat-utensil containing artificial mixed soil. Length of root and stalk of the above ground tissues was measured after treatment for 6 days. The inhibition ratio is used to describe the control efficiency of the compounds. Dosage (activity ingredient) for each compound is 50 ppm and 100 ppm. Purified compounds were dissolved in 100 μL *N,N*-dimethylformamide with the addition of 30 mL water and 1% Tween 80 to give 50 ppm and 100 ppm concentration for each sample. Then it was sprayed using a laboratory belt sprayer delivering at 3.0 mL-spray-volume. For comparison, another flat-utensil containing the mixture of the same amount of water, *N,N*-dimethylformamide and Tween 80 was sprayed as control. Triplicate each treatment. Activity numbers represent percent displaying herbicidal damage as compared to control. The inhibition ratio is calculated by the following equation:

$$\text{Inhibition ration} = 1 - \frac{\text{comparison}}{\text{treatment}} \times 100\%$$

3. Results and discussion

3.1. Synthesis of 2H-[1,2,4]thiadiazolo[2,3-a]pyrimidine derivatives (5a–f) and characterization

Firstly, *S*(−)-2-(4-chlorophenyl)-3-methylbutyric acid **1** was acylated by $SOCl_2$ followed by isothiocyanation and coupling reactions with 4,6-disubstituted-2-amino-pyrimidine **3a**–**f** to give *N*′-(4,6-disubstituted-pyrimid-2-yl)-*N*-[2-(4-chlorophenyl)-3-methylbutyric)]-thiourea **4a**–**f** in moderate yield. Then the title compounds **5a**–**f** were successfully obtained using bromine as cyclic reagent with overall 50–60% yield. Compounds **5a**–**f** were characterized by ^{1}H NMR, EI and elemental analysis. All results are in full agreement with the proposed structures. For example, the singlet signal at 6.87 ppm (pyrimidine) and the doublet signal at 0.9 and 1.1 ppm ($CH(CH_3)_2$) of ^{1}H NMR spectra suggest that compound 5e is consistent with its structure, and MS matches the calculated values to show the $[M]^+$ ions as 376.1. The results of elemental analyses are in good agreement with those calculated for the suggested formula. The melting points are sharp indicating the purity of these compounds.

3.2. Biological activity of target compounds

The herbicidal activities of the target compounds were evaluated against a variety of weeds by flat-utensil method according with the standard bioactivity test procedures of Shanghai Academy of Agricultural Sciences in China. The results were summarized in Table 1.

Table 1 The inhibition percentage of the target compounds against various weeds.

Compounds	Concentration (ppm)	*Echinochloa crusgallis* L.		*Sorghum bicolort*		*Digitaria sanguinalis* L.		*Chenopodium serotinum* L.		*Amaranthus retroflexus* L.	
		Stalk	Root	Stalk	Root	Stalk	Root	Stalk	Root	Stalk	Root
(±)**5a**	50	20	0	0	0	40	30	40	35	10	20
	100	25	10	10	0	60	70	70	60	20	50
(±)**5b**	50	30	0	10	0	35	30	20	20	30	20
	100	30	0	20	0	60	60	50	50	30	45
5a	50	50	30	20	20	55	45	50	50	50	50
	100	80	30	25	20	90	80	80	85	95	100
5b	50	40	20	25	20	50	40	90	90	45	40
	100	70	20	40	50	90	80	90	90	80	95
5c	50	40	30	20	20	0	0	20	30	50	45
	100	75	50	30	20	10	0	40	60	75	80
5d	50	60	80	60	60	0	0	10	10	0	0
	100	70	100	80	80	10	10	20	10	20	30
5e	50	30	70	35	30	10	20	70	50	60	50
	100	40	80	40	30	10	25	100	80	95	90
5f	50	10	70	10	20	30	30	80	80	90	85
	100	30	90	20	40	30	40	85	90	100	100

From Table 1, we could find that most of the target compounds had moderate inhibitory activities and selectivities against root and stalk of monocotyledon and dicotyledon plants. Compounds **5a** and **5f** showed the highest inhibitory activities against root and stalk of *Amaranthus retroflexus* L. in higher concentration (1.0×10^{-4} μg/mL), while compounds **5d** and **5e** showed good activities against root of *Echinochloa crusgallis* L. and stalk of *Chenopodium serotinum* L., respectively. It was worth noting that the chiral target compounds showed improved herbicidal activities to some extent over their racemic counterparts (such as **5a** versus (±)**5a** and **5b** versus (±)**5b**) against a variety of tested weeds, which might be contributed by the introduction of chiral active unit. Further structure–herbicidal activity relationships about the designed compounds were under the way. The present work provided a novel class of chirality-based thiadiazolopyrimidine derivatives with potential herbicidal activities for further optimization.

4. Conclusion

In the present work, we design and discover a new class of *S*(−)-2-(4-chlorophenyl)-3-methylbutyric acid thiadiazolopyrimidine conjugates with potential herbicidal activities. The preliminary results showed that most of the target compounds had moderate inhibitory activities and selectivities against root and stalk of monocotyledon and dicotyledon plants. Furthermore, the chiral target compounds showed improved herbicidal activities to some extent over their racemic counterparts against a variety of tested weeds, which might be contributed by the introduction of chiral active unit.

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