Synthesis and biological activity of *N'*-(substituted pyrimidin-2-yl)-*N*-dichlorochrysanthemoyl thioureas and their fused heterocyclic compounds

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Five *N'*-(substituted pyrimidin-2-yl)-*N*-dichlorochrysanthemoyl thioureas (**5a-5e**) were synthesized from corresponding dichlorochrysanthemic acid in three steps. And two dichlorochrysanthemoylimino-2*H*-1,2,4-thiadiazolo[2,3-*a*]pyrimidines were prepared by oxidizing cyclization of **5a**, **5b**. The structures of these novel target compounds were confirmed by IR, ¹H NMR and elemental analyses. The preliminary biological activity tests indicated that some target compounds had better insecticidal activity, fungicidal activity and so on multiple efficacies.

The acyl thiourea compounds are well known for their better pesticidal activity, fungicidal activity, antivirus activity and regulating activity for plant growth^{1,2}. In addition, they are very important intermediates in organic synthesis³⁻⁵. During recent years, the pseudo cinerins have been widely developed as chiral pesticides with high efficiency, have good pesticidal activity⁶ and regulating activity for plant growth as well⁷. In the process of searching for new active materials and precursor compounds, we adopted the method of combining active groups together to synthesize *N'*-(substituted pyrimidin-2-yl)-*N*-dichlorochrysanthemoyl thioureas (**5a-5e**) by bring dichlorochrysanthemic acid in the acyl thiourea structure with pyrimidine ring. According to the survey of literature, 2*H*-1,2,4-thiadiazolo[2,3-*a*]pyrimidine derivatives are another noticeable ALS inhibitor after the advent of sulfonylurea herbicides, which have comparative herbicidal activity, yet with superior selectivity⁸⁻¹¹. Two dichlorochrysanthemoylimino-2*H*-1,2,4-thiadiazolo[2,3-*a*]pyrimidines (**6a**, **6b**) were prepared from (**5a**, **5b**) by employing Br₂ as the oxidant^{12,13}. We expected to make full use of each active group by linking acyl thiourea with 2*H*-1,2,4-thiadiazolo[2,3-*a*]pyrimidine effectively. Moreover, these compounds contain an inherently weak N-S bond which can benefit plant's absorption and metabolism. In fact, this is where their good selectivity exists. The structures of these novel target compounds were confirmed by IR, ¹H NMR and elemental analyses. The preliminary biological activity tests indicated that some target compounds had better insecticidal activity, fungicidal activity and so on multiple efficacies.

The process for synthesis of target compounds is in Scheme 1.

Scheme 1

Experimental

Reagents and apparatus :

All precursor substances are commercial products of chemical or analytical grade purity. Sulfuryl chloride was redistilled before use and potassium thiocyanate was dried before use. 2-Amino-4,6-disubstituted pyrimidines (**4**) were prepared by the literature method¹⁴. Dichlorochrysanthemic acid is a white solid (m.p. 60–62°C).

The melting point was determined on an XT4A micro digital melting point apparatus, and were uncorrected. The C, H and N analyses were repeated twice by elemental microanalyses. The IR spectra were recorded in the region 4000–400 cm⁻¹ KBr discs on a Nicolet 5DX FT-IR spectrophotometer. The ¹H NMR spectra were obtained on a Varian-300-54 spectrometer in d₆-DMSO using TMS as internal reference.

Procedure :

The procedure for the synthesis of the target compounds

5a-5e, 6a-6b is as follows :

Dichlorochrylsanthemic acid (0.01 mol) as dissolved in petroleum ether (5 mL) in a dried round-bottomed flask containing a magnetic stirrer, and dripped the mixture of sulfonyl chloride (0.015 mol) and petroleum ether (5 mL) at about 0°C, after refluxing for 2 h, the system was left to cool at room temperature. The petroleum ether and excessive sulfonyl chloride were removed under reduced pressure to give a clear solution of dichlorochrylsanthemoyl chloride **2**, which was added to a solution of potassium thiocyanate (0.015 mol) in 10 mL of absolute acetonitrile. The reaction mixture was stirred and refluxed for about 45 min, the precipitate in the solution was filtered off to yield an orange-red solution **3**. Then equimolar quantity of 4,6-disubstituted-2-amino pyrimidine **4** was added to react under refluxed temperature for about 3 h. In the end, the resulting precipitate was collected by filtration and recrystallized from DMF-EtOH-H₂O to yield the target compound **5**. To a solution of compound **5a, 5b** in 15 ml of CHCl₃, equimolar quantity of bromine was drop added at water-ice bath. After addition, the flask with the reaction mixture was stirred at room temperature for about several hours, and the process of the reaction was monitored by TLC. At the end of the reaction, the resulting precipitate was collected by filtration and recrystallized from DMF-EtOH-H₂O to yield target compound **6a, 6b**.

Biological activity test :

The biological activity was evaluated with the standard bioactivity test procedures of Shanghai Branch of National Pesticide R & D South Central in China. All the target compounds were tested by their herbicidal activity, insecticidal activity and fungicidal activity.

Results and discussion

Characterization of target molecules :

N'-(Substituted pyrimidin-2-yl)-N-dichlorochrylsanthemoyl thioureas (5a-5e) :

TM 5a Yield 78%, m.p. 159–162°C (Found : C, 44.69; H, 4.27; N, 13.60. Calcd. for C₁₅H₁₈Cl₂N₄O₃S : C, 44.45; H, 4.48; N, 13.82%); IR (cm⁻¹) 3221, 2969 (N–H), 1701 (C=O), 1607 (C=N), 1235 (C=S); ¹H NMR (*d*₆-DMSO) 1.22 (3H, s, CH₃), 1.30 (3H, s, CH₃), 2.25 (1H, q, CH), 2.49 (1H, d, CH), 4.00 (6H, s, 2OCH₃), 6.05 (1H, s, Py-5'-H), 6.10 (1H, d, C=CH), 11.95 (1H, s, NH), 12.60 (1H, s, NH).

TM 5b Yield 74%, m.p. 128–132°C (Found: C, 47.33; H, 5.36; N, 12.71. Calcd. for C₁₇H₂₂Cl₂N₄O₃S : C, 47.12; H, 5.12; N, 12.93%); IR (cm⁻¹) 3232, 2791 (N–H), 1702 (C=O), 1604 (C=N), 1225 (C=S); ¹H NMR (*d*₆-DMSO)

1.20–1.40 (12H, m, 2OCH₂CH₃ and 2CH₃), 2.20 (1H, q, CH), 2.50 (1H, d, CH), 4.28 (4H, q, 2OCH₂CH₃), 5.75 (1H, d, C=CH), 5.80 (1H, s, Py-5'-H), 8.50 (1H, s, NH), 13.40 (1H, s, NH).

TM 5c Yield 80%, m.p. 180–181°C (Found : C, 48.02; H, 4.99; N, 14.88. Calcd. for C₁₅H₁₈Cl₂N₄OS : C, 48.26; H, 4.86; N, 15.01%); IR (cm⁻¹) 3174, 2951 (N–H), 1705 (C=O), 1599 (C=N), 1239 (C=S); ¹H NMR (*d*₆-DMSO) 1.20 (6H, s, CH₃), 1.25 (6H, s, CH₃), 2.20 (1H, q, CH), 2.43 (1H, d, CH), 6.42 (1H, d, C=CH), 6.80 (1H, s, Py-5'-H), 8.80 (1H, s, NH), 14.00 (1H, s, NH).

TM 5d Yield 84%, m.p. 177–179°C (Found : C, 46.48; H, 4.44; N, 14.16. Calcd. for C₁₅H₁₈Cl₂N₄O₂S : C, 46.28; H, 4.66; N, 14.39%); IR (cm⁻¹) 3186, 2954 (N–H), 1704 (C=O), 1600 (C=N), 1232 (C=S); ¹H NMR (*d*₆-DMSO) 1.22 (3H, s, CH₃), 1.29 (3H, s, CH₃), 2.22 (1H, q, CH), 2.45 (3H, s, CH₃), 2.50 (1H, d, CH), 3.93 (3H, s, OCH₃), 6.23 (1H, s, Py-5'-H), 6.40 (1H, d, C=CH), 8.90 (1H, s, NH), 13.40 (1H, s, NH).

TM 5e Yield 83%, m.p. 133–135°C (Found : C, 47.83; H, 5.21; N, 14.07. Calcd. for C₁₆H₂₀Cl₂N₄O₂S : C, 47.65; H, 5.00; N, 13.89%); IR (cm⁻¹) 3218, 2973 (N–H), 1689 (C=O), 1605 (C=N), 1240 (C=S); ¹H NMR (*d*₆-DMSO) 1.22–1.40 (9H, m, OCH₂CH₃ and 2CH₃), 2.23 (1H, q, CH), 2.48 (1H, d, CH), 2.50 (3H, s, CH₃), 4.50 (2H, q, OCH₂CH₃), 6.40 (1H, d, C=CH), 6.65 (1H, s, Py-5'-H), 8.50 (1H, s, NH), 13.80 (1H, s, NH).

Dichlorochrylsanthemoylimino-2H-1,2,4-thiadiazolo[2,3-a]pyrimidines (6a-6b) :

TM 6a Yield 78%, m.p. 131–132°C (Found : C, 44.50; H, 3.72; N, 13.76. Calcd. for C₁₅H₁₆Cl₂N₄O₃S : C, 44.67; H, 3.97; N, 13.90%); IR (cm⁻¹) 1720 (C=O), 1604 (C=N); ¹H NMR (*d*₆-DMSO) 1.24 (3H, s, CH₃), 1.28 (3H, s, CH₃), 2.30 (1H, m, CH), 3.82 (3H, s, OCH₃), 3.96 (3H, s, OCH₃), 5.40 (1H, s, Py-5'-H), 6.18 (1H, q, CH), 8.28 (1H, s, C=CH).

TM 6b Yield 82%, m.p. 126–129°C (Found : C, 47.54; H, 4.42; N, 12.70. Calcd. for C₁₇H₂₀Cl₂N₄O₃S : C, 47.33; H, 4.64; N, 12.99%); IR (cm⁻¹) 1728 (C=O), 1600 (C=N); ¹H NMR (*d*₆-DMSO) 1.16–1.32 (12H, m, 2CH₃ and 2OCH₂CH₃), 2.23 (1H, m, CH), 4.28 (2H, q, OCH₂CH₃), 4.35 (2H, q, OCH₂CH₃), 5.35 (1H, s, Py 5'-H), 5.78 (1H, q, CH), 7.90 (1H, s, C=CH).

The structures of all newly synthesized compounds **5, 6** were assigned on the basis of their elemental analyses and spectroscopic data, IR and ¹H NMR. All compounds of series **5** had strong N–H absorption at about 3220 cm⁻¹, and at 2960 cm⁻¹, they also had absorption band. The IR (KBr) spectrum displayed absorption at about 1690–1710 cm⁻¹,

1600 cm^{-1} and 1200 cm^{-1} , which were assigned to C=O, C=N and C=S functions respectively. The medium-strong $\nu_{\text{C=O}}$ band in the IR spectra of all the compounds of series **5** appeared at 1690–1710 cm^{-1} , apparently decreasing in wavenumber compared with the ordinary carbonyl absorption (1730 cm^{-1}). The formation of H-bond inside these molecules lead the magnification of their polarity, so the strength of their double bond decreased, and their absorption moved to lower wavenumber. This is not possible in compounds of series **6**, hence, their absorption of C=O was at comparatively higher wavenumber. Even though, there was delocalized pi-bond in these compounds, the wavenumber was not so high as the ordinary carbonyl, at about 1720 cm^{-1} . The ^1H NMR (d_6 -DMSO) spectrum exhibited the quartet and doublet signals at about δ 2.20 and δ 2.45 were assigned to two protons of the three-membered ring. That's because that the hardly rotating single bonds of the three-membered ring made two different protons. Similarly, the two methyls on the three-membered ring had different absorption, but sometimes they overlapped together. The double bond C=C was substituted by chlorines, the chemical shift of its protons appeared at about 6.35 ppm. Most of the compounds of series **5** exhibited signals at 8.80–9.15 ppm and 13.40–14.00 ppm. These are assigned to the

Table 1. Insecticidal activity

Compd.	Conc. (ppm)	Test insects	Mortality			Mortality rate 72h (%)
			24 h	48 h	72 h	
5a	50	43	15	28	35	81.40
5b	50	22	0	0	6	27.27
5d	50	30	8	26	30	100.00
6a	50	23	3	15	21	91.30

two N–H. The chemical shift of the proton of pyrimidine ring (Py-5'-H) can change greatly, just relied on the different substituents.

The biological activities of all the newly synthesized compounds were also evaluated. The preliminary test showed that some target compounds had better insecticidal activity, fungicidal activity. The insecticidal and fungicidal activities of some active compounds are given in the following Tables.

The mortality rate of compound **5d** could reach 100% in 72 h. The excellent insecticidal activity implied its prosperous future on the basis of deep research. Meanwhile, the

Table 2. Fungicidal activity

Compd.	Conc. (mg/L)	<i>Colletotrichum lagenarium</i> (%)	<i>Sphaerotheca fuliginea</i> (%)
5a	1000	62	60
5b	1000	84	60
5d	1000	77	50

experiment showed that compound **6a** had better insecticidal activity.

According to the results in Table 2, the caution of compounds **5b** and **5d** against *Colletotrichum lagenarium* got 84% and 77% respectively, the better efficiency of these compounds indicated the value of further experiments.

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