Chinese Chemical Letters 25 (2014) 137–140

Contents lists available at ScienceDirect

Chinese Chemical Letters

journal homepage: www.elsevier.com/locate/cclet

Original article

Synthesis and acaricidal activity of strobilurin-pyrimidine derivatives

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ARTICLE INFO

Article history:
Received 15 May 2013
Received in revised form 10 September 2013
Accepted 13 September 2013
Available online 12 November 2013

Keywords:
Strobilurin-pyrimidine
Acaricidal activity
Intermediate derivatization method
Pyriminostrobin

ABSTRACT

Pyriminostrobin, a new acaricide, was discovered in our previous studies. Because introducing fluorine into organic compounds can increase bioactivity, pyriminostrobin was modified as a series of strobilurin-pyrimidine derivatives for biological screening. The compounds were characterized by ^{1}H NMR, MS and elemental analysis. Preliminary bioassays demonstrated that compounds **7e** and **7i** exhibited significant control against *Tetranychus cinnabarinus* (Boisd.) at 0.625 mg L^{-1}, and their acaricidal potencies were higher than pyriminostrobin in a greenhouse. The relationship between structure and acaricidal activity was also studied.

1. Introduction

Pyriminostrobin (SYP-11277), a novel acaricide, was reported in our previous work [1,2]. The discovery of pyriminostrobin was outlined in Fig. 1, in which the lead compound was altered by the intermediate derivatization method [3–5], and then optimized to synthesize pyriminostrobin. There has been increasing interest in the introduction of fluorine or appropriate fluorinated functional groups into organic compounds in recent years [6–12]. Incorporation of one or several fluorine atoms into organic molecules can enhance their biological potency due to the intrinsic properties of the fluorine atom. These include having the highest electronegativity, a small atomic radius, high thermal stability and lipophilicity, which could provide easier absorption and transportation of organic molecules within biological systems [12]. Thus, substitution of fluorine into a potential drug molecule is an important strategy in drug and agrochemical development [10].

The above-mentioned biological and synthetic significance prompted us to carry out the synthesis of some new strobilurin-pyrimidine derivatives **7** with fluorine substitution, which showed promising acaricidal activity in addition to its fungicidal activity [13].

2. Experimental

The general synthetic scheme for representative compounds **7a–k** is shown in Scheme 1. Reaction yields were not optimized, and each new compound was identified and verified by ^{1}H NMR, MS and elemental analyses. The strobilurin derivatives containing pyrimidine moieties have been reported in previous works [1,14]. Compounds **7a–k** were synthesized by the same synthetic methods. Substituted phenyl guanidines (**2**) were prepared from substituted anilines (**1**) and cyanamide under acidic conditions. Ethyl 4,4,4-trifluoro-2-methyl-3-oxobutanoate was obtained from ethyl 4,4,4-trifluoro-3-oxobutanoate following procedures in the literature [15].

*General procedure for the synthesis of intermediate substituted phenyl guanidines (**2**)*: Substituted anilines (**1**, 0.02 mol) was added to concentrated hydrochloric acid (0.02 mol). The mixture was heated to 85 °C and cyanamide (0.024 mol) was added portion-wise. Heating continued for 5 h before the reaction solution was cooled to 60 °C, and then sodium carbonate (0.01 mol) water solution was added. After continued cooling, the mixture was filtered to obtain the crude substituted phenyl guanidine carbonates **2**.

*General procedure for the synthesis of intermediate pyrimidin-4(3H)-one (**5**)*: Substituted phenyl guanidine carbonates (**2**, 0.01 mol) and β-keto esters (**3** or **4**, 0.02 mol) were added to toluene (30 mL), and the mixture was heated to reflux with a Dean Stark trap until all water was azeotropically removed. The reaction

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1001-8417/$ – see front matter
http://dx.doi.org/10.1016/j.cclet.2013.10.006

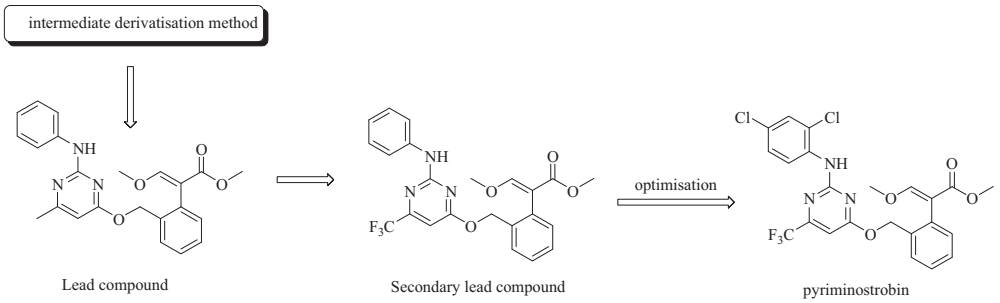


Fig. 1. The discovery of pyriminostrobin.

solution was cooled and then filtered. The solid was washed with toluene and dried as intermediate **5**.

*Synthesis of (E)-methyl 2-(2-(((2-((2,4-difluorophenyl)amino)-6-(trifluoromethyl)pyrimidin-4-yl)oxy)methyl)phenyl)-3-methoxyacrylate (***7e***)*: A mixture of 2-((2,4-difluorophenyl)amino)-6-(trifluoromethyl)pyrimidin-4(3H)-one (**5e**) (0.35 g, 1.2 mmol), (*E*)-methyl 2-(2-(chloromethyl)phenyl)-3-methoxyacrylate (**6**) (0.30 g, 1.25 mmol) and K_2CO_3 (0.33 g, 2.4 mmol) in DMF (15 mL) was stirred and heated at 80 °C for 8 h. The reaction mixture was then cooled, diluted with water (100 mL), and extracted with ethyl acetate (3 × 25 mL). The organic layer was separated, washed with saturated brine, dried over $MgSO_4$, and filtered. The filtrate was evaporated, and the crude product was purified *via* silica gel column chromatography using a 1:10 (v/v) mixture of ethyl acetate and petroleum ether (boiling point range: 60–90 °C) as the eluent to obtain 0.44 g of white crystals. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.28 (s, 1H, Ph′-NH-Py), 7.59 (s, 1H, C═CH), 7.48–6.90 (m, 7H, Ph′-3H + Ph-4H), 6.54 (s, 1H, Py-5-H), 5.31 (s, 2H, $PhCH_2O$), 3.80 (s, 3H, $COOCH_3$), 3.70 (s, 3H, ═C–OCH_3); Mol. wt: 495.40. LC–MS: *m/z* 494.2 $[M-H]^-$, 496.3 $[M+H]^+$, Anal. calcd. (%) for $C_{23}H_{18}F_5N_3O_4$: C, 55.76; H, 3.66; N, 8.48; Found: C, 55.78; H, 3.66; N, 8.52.

7a: White solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.86 (s, 1H, Ph′-NH-Py), 7.78 (d, 2H, Ph′-2,6-2H, *J* = 9.0 Hz), 7.62 (s, 1H, C═CH), 7.57 (d, 2H, Ph′-3,5-2H, *J* = 9.0 Hz), 7.48 (m, 1H, Ph-6-H), 7.35 (m, 2H, Ph-3,5-2H), 7.20 (m, 1H, Ph-4-H), 6.57 (s, 1H, Py-5-H), 5.35 (s, 2H, $PhCH_2O$), 3.81 (s, 3H, $COOCH_3$), 3.74 (s, 3H, ═C–OCH_3); Mol. wt: 527.42. LC–MS: *m/z* 526.5 $[M-H]^-$, 528.3 $[M+H]^+$, Anal. calcd. (%) for $C_{24}H_{19}F_6N_3O_4$: C, 54.65; H, 3.63; N, 7.97; Found: C, 54.69; H, 3.66; N, 7.98.

7b: White solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.06 (br s, 1H, Ph′-NH-Py), 7.81–7.18 (m, 9H, Ph′-4H + Ph-4H + C═CH), 6.53 (s, 1H, Py-5-H), 5.30 (s, 2H, $PhCH_2O$), 3.80 (s, 3H, $COOCH_3$), 3.73 (s, 3H, ═C–OCH_3); Mol. wt: 527.42. LC–MS: *m/z* 526.5 $[M-H]^-$, 528.3 $[M+H]^+$, Anal. calcd. (%) for $C_{24}H_{19}F_6N_3O_4$: C, 54.65; H, 3.63; N, 7.97; Found: C, 54.66; H, 3.65; N, 7.98.

7c: White solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.40 (s, 1H, Ph′-NH-Py), 7.58 (s, 1H, C═CH), 7.55 (m, 2H, Ph′-2,6-2H), 7.50 (m, 1H, Ph-6-H), 7.37 (m, 2H, Ph-3,5-2H), 7.31 (m, 2H, Ph′-3,5-2H), 7.20 (m, H, Ph-4-H), 7.00 (s, 1H, Py-5-H), 5.40 (s, 2H, $PhCH_2O$), 3.80 (s, 3H, $COOCH_3$), 3.68 (s, 3H, ═C–OCH_3); Mol. wt: 477.41. LC–MS: *m/z* 476.5 $[M-H]^-$, 478.4 $[M+H]^+$, Anal. calcd. (%) for $C_{23}H_{19}F_4N_3O_4$: C, 57.86; H, 4.01; N, 8.80; Found: C, 57.79; H, 4.00; N, 8.82.

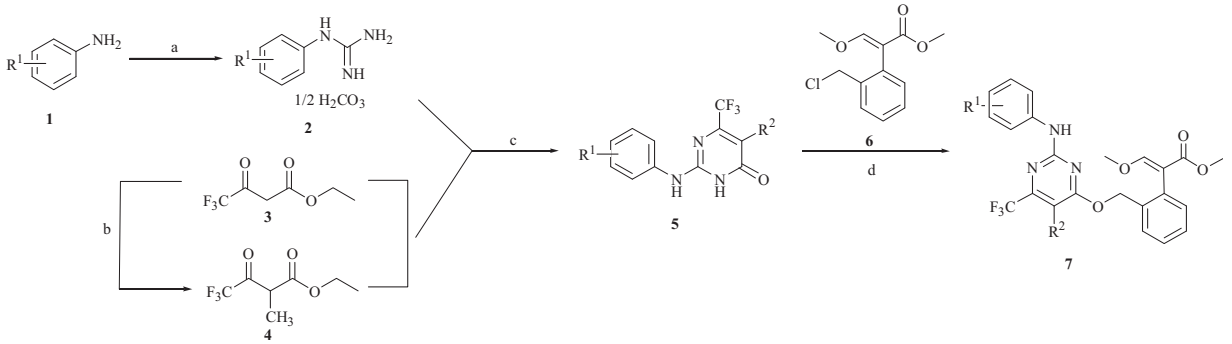
7d: White solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.82 (s, 1H, Ph′-NH-Py), 7.61 (s, 1H, C═CH), 7.48–7.06 (m, 7H, Ph′-3H + Ph-4H), 6.53 (s, 1H, Py-5-H), 5.34 (s, 2H, $PhCH_2O$), 3.82 (s, 3H, $COOCH_3$), 3.73 (s, 3H, ═C–OCH_3); Mol. wt: 477.41. LC–MS: *m/z* 476.5 $[M-H]^-$, 478.4 $[M+H]^+$, Anal. calcd. (%) for $C_{23}H_{19}F_4N_3O_4$: C, 57.86; H, 4.01; N, 8.80; Found: C, 57.80; H, 4.02; N, 8.82.

7f: White solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.37 (s, 1H, Ph′-NH-Py), 7.59 (s, 1H, C═CH), 7.50–7.12 (m, 7H, Ph′-3H + Ph-4H), 6.56 (s, 1H, Py-5-H), 5.33 (s, 2H, $PhCH_2O$), 3.80 (s, 3H, $COOCH_3$), 3.70 (s, 3H, ═C–OCH_3); Mol. wt: 511.85. LC–MS: *m/z* 510.7 $[M-H]^-$, 512.8 $[M+H]^+$, Anal. calcd. (%) for $C_{23}H_{18}ClF_4N_3O_4$: C, 53.97; H, 3.54; N, 8.21; Found: C, 53.91; H, 3.55; N, 8.21.

7g: White solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.06 (s, 1H, Ph′-NH-Py), 7.81–7.18 (m, 9H, Ph′-4H + Ph-4H + C═CH), 6.53 (s, 1H, Py-5-H), 5.30 (s, 2H, $PhCH_2O$), 3.80 (s, 3H, $COOCH_3$), 3.73 (s, 3H, ═C–OCH_3); Mol. wt: 511.85. LC–MS: *m/z* 510.7 $[M-H]^-$, 512.8 $[M+H]^+$, Anal. calcd. (%) for $C_{23}H_{18}$–$ClF_4N_3O_4$: C, 53.97; H, 3.54; N, 8.21; Found: C, 53.92; H, 3.50; N, 8.18.

7h: White solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.54 (s, 1H, C═CH), 7.00–7.33 (m, 7H, Ph′-3H + Ph-4H), 6.71 (br s, 1H, Ph′-NH-Py), 6.48 (s, 1H, Py-5-H), 5.16 (s, 2H, $PhCH_2O$), 3.75 (s, 3H, $COOCH_3$), 3.67 (s, 3H, ═C–OCH_3); Mol. wt: 495.40. LC–MS: *m/z* 494.2 $[M-H]^-$, 496.3 $[M+H]^+$, Anal. calcd. (%) for $C_{23}H_{18}F_5N_3O_4$: C, 55.76; H, 3.66; N, 8.48; Found: C, 55.78; H, 3.68; N, 8.50.

7i: White solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.06 (br s, 1H, Ph′-NH-Py), 7.59 (s, 1H, C═CH), 7.48–6.98 (m, 6H, Ph′-2H + Ph-4H), 6.57 (s, 1H, Py-5-H), 5.31 (s, 2H, $PhCH_2O$), 3.81 (s, 3H, $COOCH_3$),

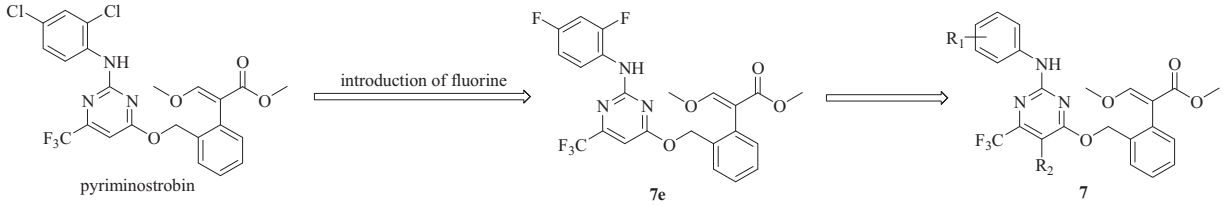


Scheme 1. Synthetic route of title compounds **7**: (a) NH_2CN, HCl, 85 °C; (b) CH_3Br, NaH, DMF; (c) toluene, reflux; and (d) K_2CO_3, DMF, 80 °C.

Table 1
Physical properties and acaricidal activity of strobilurin-pyrimidine analogs **7**.

Compd.	R^1	R^2	Mp (°C)	Yield (%)	*T. cinnabarinus* (% mortality at given concentration mg L^{-1})					
					40	10	5	2.5	1.25	0.625
7a	4-CF_3	H	149–151	74.3	0	0	/	/	/	/
7b	3-CF_3	H	138–140	68.8	100	30	/	/	/	/
7c	4-F	H	136–138	75.1	0	0	/	/	/	/
7d	2-F	H	142–144	59.9	100	100	90	40	20	/
7e	2,4-F_2	H	105–107	75.0	100	100	100	100	98	90
7f	2-F-4-Cl	H	118–120	65.9	100	100	98	92	86	62
7g	3-Cl-4-F	H	135–137	69.8	95	90	40	10	0	/
7h	2,6-F_2	H	146–149	70.1	0	0	/	/	/	/
7i	2,3,4-F_3	H	129–130	68.9	100	100	100	100	100	95
7j	2,4-F_2	CH_3	129–131	58.0	100	100	40	0	0	/
7k	2,3,4-F_3	CH_3	156–158	48.6	100	99	20	11	0	/
Pyriminostrobin					100	100	100	98	90	62
Fluacrypyrim					100	95	94	65	30	/

/, not tested.



(1) Sequence of the substitution patterns R^1: 2,3,4-3F, 2,4-2F > 2-F-4-Cl > 2-F > 3-Cl-4-F > 3-CF_3 >> 4-CF_3, 4-F, 2,6-2F
(2) Sequence of the substitution patterns R^2: H > CH_3

Fig. 2. Optimizations of compound **7e**.

3.71 (s, 3H, =C–OCH_3); Mol. wt: 513.39. LC–MS: *m/z* 512.4 $[M-H]^-$, 514.7 $[M+H]^+$, Anal. calcd. (%) for $C_{23}H_{17}F_6N_3O_4$: C, 53.81; H, 3.34; N, 8.18; Found: C, 53.78; H, 3.40; N, 8.12.

7j: White solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.40 (br s, 1H, Ph′-NH-Ph), 7.44–6.82 (m, 7H, Ph′-3H + Ph-4H), 6.03 (br s, 1H, NH), 5.51 (s, 2H, $PhCH_2O$), 3.67 (s, 3H, =N–OCH_3), 2.93 (d, J = 4.8 Hz, 3H, $NHCH_3$), 2.24 (s, 3H, CH_3); Mol. wt: 509.43. LC–MS: *m/z* 509.2 $[M-H]^-$, 511.4 $[M+H]^+$, Anal. calcd. (%) for $C_{24}H_{20}F_5N_3O_4$: C, 56.58; H, 3.96; N, 8.25; Found: C, 56.60; H, 3.99; N, 8.21.

7k: White solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.20 (br s, 1H, Ph′-NH-Py), 7.40–6.91 (m, 6H, Ph′-2H + Ph-4H), 6.05 (br s, H, NH), 5.49 (s, 2H, $PhCH_2O$), 3.68 (s, 3H, =N–OCH_3), 2.94 (d, J = 4.8 Hz, 3H, $NHCH_3$), 2.25 (s, 3H, CH_3); Mol. wt: 527.42. LC–MS: *m/z* 526.3 $[M-H]^-$, 528.5 $[M+H]^+$, Anal. calcd. (%) for $C_{24}H_{19}F_6N_3O_4$: C, 54.65; H, 3.63; N, 7.97; Found: C, 54.66; H, 3.65; N, 7.94.

3. Results and discussion

As shown in Scheme 1, the target compounds were readily synthesized. Table 1 summarized the physical characteristics, yields, and acaricidal activities of all strobilurin-pyrimidine analogs. Two fluorines were introduced into pyriminostrobin to replace the chlorines to produce **7e**, a more potent acaricidal compound with 90% mortality against *Tetranychus cinnabarinus* at 0.625 mg L^{-1}.

The current investigation studied the effects of incorporating various fluorine substitution patterns in compound **7e**. Also, the effects of replacement of the hydrogen by a methyl group in the 5-position of the pyrimidine scaffold were investigated. The acaricidal biological activities were evaluated, and the results furthered understanding of the structure–activity profile (Fig. 2).

The 2-phenylamino motif was modified with various fluorine substituent phenyl amines, including mono-substituted, disubstituted, and trisubstituted phenyl rings. Some substitution patterns, such as 4-CF_3, 4-F, 2,6-2F, were not active at all at 40 mg L^{-1}. A number of disubstituted and trisubstituted compounds exhibited potent acaricidal activity, though, with two compounds (**7e** and **7i**) proving much more active than the reference compound fluacrypyrim [16] at 0.625 mg L^{-1}. However, 5-methylation of the pyrimidine ring (**7j** and **7k**) greatly reduced the compound's potency against *T. cinnabarinus* (*vs* **7e** and **7i**). This result demonstrated that the 5-hydrogen of the pyrimidine ring is both necessary and an optimal substituent for maintaining the compounds' activity. Two highly active acaricidal compounds were identified in this study. As shown in Table 1, they exhibited greater mortality rates than 90% at doses of 0.625 mg L^{-1} against *T. cinnabarinus*. Anticipating agricultural utilization, two compounds, **7e** and **7i,** were chosen as candidates for extensive greenhouse bioassays on larvae and eggs of *T. cinnabarinus*. Both of them showed potency consistent with pyriminostrobin against larvae, and weaker potency than pyriminostrobin against eggs, as shown in (Table 2).

4. Conclusion

In order to introduce fluorine into pyriminostrobin to improve its bio-activity, a series of strobilurin-pyrimidine derivatives

Table 2
Acaricidal activity of **7e** and **7i** against *T. cinnabarinus*.

Compd.	*T. Cinnabarinus*	(% mortality at given concentration mg L^{-1})		
		10	2.5	0.625
7e	Larvae	100	98	77
	Eggs	100	70	25
7i	Larvae	100	100	100
	Eggs	75	20	10
Pyriminostrobin	Larvae	100	100	96
	Eggs	100	100	20

(**7a**–**k**) were synthesized. The highly active compound **7e** was discovered by using fluorine to replace chlorine of pyriminostrobin, after which the 2,4-2F-phenylamine moiety was modified into various fluorine substitution patterns (**7a**–**d**, **7f**–**k**). Compounds **7e** and **7i** were shown to be more potent than pyriminostrobin against *T. cinnabarinus* at 0.625 mg L^{-1}.

Acknowledgments

We are grateful to the Outstanding Young Scholarship from the National Natural Science Foundation of China (No. 30825043), NSFC (No. 21172202), and the Outstanding Scholar Foundation of Henan Province (No. 094100510019) for financial support. This project was also supported by the National Key Basic Research Program of China (973 Program) (Nos. 2010CB126105 and 2012CB724501) and the National Key Technology Support Program during the 12th Five-Year Plan Period (Nos. 2011BAE06B00, 2011BAE06B01, 2011BAE06B02, 2011BAE06B03 and 2011BAE06B05).

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