Regular Article

Ethyl Cinnamate Derivatives as Promising High-Efficient Acaricides against *Psoroptes cuniculi*: Synthesis, Bioactivity and Structure–Activity Relationship

Bingyu Zhang,[a,#] Chao Lv,[a,#] Weibo Li,[b] Zhiming Cui,[a] Dongdong Chen,[a] Fangjun Cao,[a] Fang Miao,*[,b] and Le Zhou*[,a]

[a] *College of Science, Northwest A&F University; Yangling, Shaanxi 712100, China: and* [b] *College of Life Science, Northwest A&F University; Yangling, Shaanxi 712100, China.*

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This paper reported the synthesis, structure–activity relationship (SAR) and acaricidal activity *in vitro* against *Psoroptes cuniculi*, a mange mite, of 25 ethyl cinnamate derivatives. All target compounds were synthesized and elucidated by means of MS, ^{1}H- and ^{13}C-NMR analysis. The results showed that 24 out of 25 tested compounds at 1.0 mg/mL demonstrated acaricidal activity in varying degrees. Among them, 6, 15, 26, 27 and 30 showed significant activity with median lethal concentration values (LC_{50}) of 89.3, 119.0, 39.2, 29.8 and 41.2 μg/mL, respectively, which were 2.1- to 8.3-fold the activity of ivermectin (LC_{50}=247.4 μg/mL), a standard drug in the treatment of *Psoroptes cuniculi*. Compared with ivermectin, with a median lethal time value (LT_{50}) of 8.9 h, 27 and 30 showed smaller LT_{50} values of 7.9 and 1.3 h, respectively, whereas 6, 15 and 26 showed slightly larger LT_{50} values of 10.6, 11.0 and 10.4 h at 4.5 μmol/mL. SARs showed that the presence of *o*-NO_2 or *m*-NO_2 on the benzene ring significantly improved the activity, whereas the introduction of a hydroxy, methoxy, acetoxy, methylenedioxy, bromo or chloro group reduced the activity. (*E*)-Cinnamates were more effective than their (*Z*)-isomer. Nevertheless, the carbon–carbon double bond in the acrylic ester moiety was proven not to be essential to improve the activity of cinnamic acid esters. Thus, the results strongly indicate that cinnamate derivatives, especially their dihydro derivatives, should be promising candidates or lead compounds for the development of novel acaricides for the effective control of animal or human acariasis.

Key words cinnamic acid ester; ethyl 3-phenylpropionate; acaricidal activity; acaricide; *Psoroptes cuniculi*

Acariasis is a skin disease caused by mites, an ectoparasite which widely occurs in animals and human. *Psoroptes cuniculi* is an animal ear mite living in the ear canals of animal and can be parasitic in sheep, horse, rabbit, goat, cattle and buffalo.[1] *Psoroptic* acariasis is a highly contagious disease, which causes intense pruritus, serous exudations, inflammation, the formation of crusts and scabs, anorexia and reduction of weight gain, or even death of animals.[2] Therefore, the infection of this mite species may severely reduce the productivity and the quality of animal products.[3]

Traditionally, organophosphates, organochlorine, pyrethrins,[4] ivermectin and abamectin[5] have been used as effective drugs for treatment and control of animal acariasis. However, the chemical control could increase resistance of target species to acaricides,[6] toxicity and environmental hazards.[7,8] These problems have made researchers' efforts to discover new effective acaricides derived from natural products due to their easy degradation in the environment, less or not remain in livestock, not being prone to resistance and relative safety for humans, animals and environment.[9]

Cinnamic acid and its ester derivatives are widely distributed in plants including cereals, legumes, oilseeds, fruits, vegetables and tea or coffee beverages.[10] Due to their common occurrence in plants and their low toxicity,[11,12] cinnamic acid derivatives have attracted much attention of many pharmacologists. In the past decades, cinnamic acid derivatives including natural, semi-synthetic and synthetic compounds had been proven to have a variety of pharmacological activities,[13] such as anticancer,[14,15] antimicrobial,[16–18] antioxidative,[18] anti-inflammatory,[15,19–21] anti-*Mycobactrium tuberculosis*,[22–24] antiviral,[25] anti-human immunodeficiency virus (HIV),[26–28] antidiabetic,[29] anticholesterolemic,[30] analgesic,[31] hepatoprotective,[32,33] immunoprotective,[34] inducing neural progenitor cell proliferation[35] and anxiolytic activity.[36] Especially, what interests us is that cinnamic acid derivatives also have significant antiparasitic activities on plasmodia,[37] *Leishmania*[38] and nematode.[39] Furthermore, the acaricidal activity of ethyl cinnamate[40] and *trans*-cinnamaldehyde[41] as an analogue of cinnamic acid were reported as well. Thus, cinnamic acid derivatives are often used as promising starting compounds for the development of new, highly effective drugs. Nevertheless, until now no systematic research on acaricidal activity of cinnamic acid esters and their structure–activity relationship (SAR) were reported.

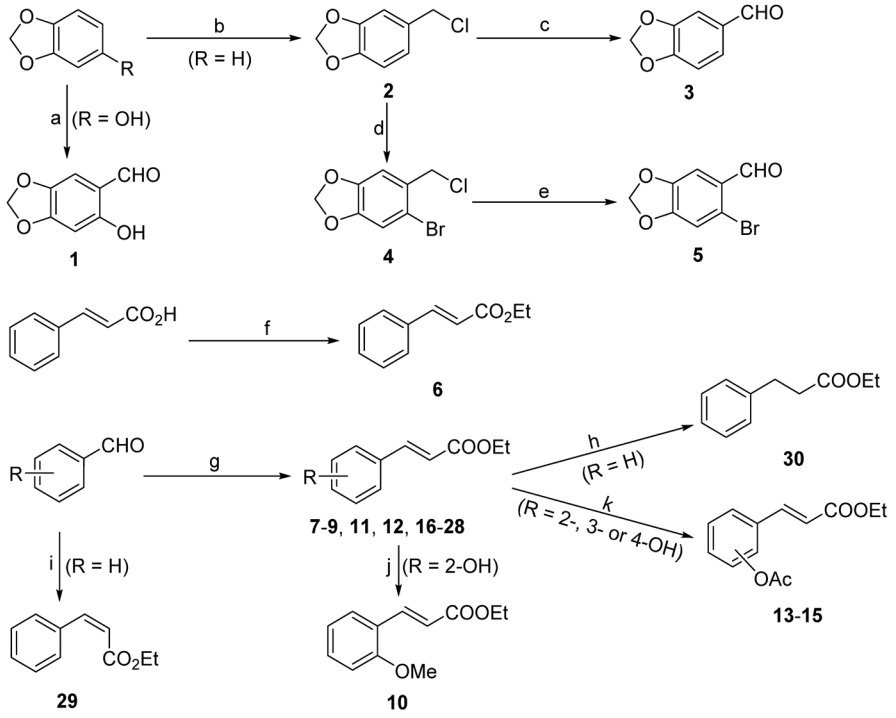
Our interest in the excellent antiparasitic activities[37–41] and the low toxicity[11,12] of cinnamic acid derivatives prompted us to explore their acaricidal activity and extend their pharmacologic activities. This investigation presented the preparation of a series of cinnamic acid ester derivatives and evaluation of their acaricidal activity against *P. cuniculi* as well as the discussion of their preliminary SAR.

Results and Discussion

Chemistry Compound **6** was obtained by esterification reaction of commercially available *trans*-cinnamic acid with ethanol using thionyl chloride as a catalyst in 95%

[#] These authors contributed equally to this work.

* To whom correspondence should be addressed. e-mail: miaofangmf@163.com; zhoulechem@nwsuaf.edu.cn



R = H; 2-OH; 3-OH; 4-OH; 3-OCH_3; 4-OCH_3; 2-OH-3-OCH_3; 4-OH-3-OCH_3; 3,4-$(OCH_3)_2$; 2,4,5-$(OCH_3)_3$; 3,4,5-$(OCH_3)_3$; 3,4-OCH_2O; 2-OH-4,5-OCH_2O; 2-Br-4,5-OCH_2O; 4-Cl; 4-Br; 2-NO_2; 3-NO_2; 4-NO_2

a. i) DMF, $POCl_3$, 0–100°C; ii) NaOAc, 100°C, 11% yield; b. Paraformaldehyde, conc. HCl, r.t., 80% yield; c. DMSO, $NaHCO_3$, 90°C, 48% yield; d. Bromine, AcOH, 92%; e. DMSO, $NaHCO_3$, 90°C, 37% yield; f. $SOCl_2$, EtOH, r.t., 95%; g. $Ph_3P{=}CHCO_2Et$. EtOH or toluene, 42–92%; h. $NaBH_4$, CuCl, MeOH, 97%; i. 2-(Bis(2-(*tert*-butyl)phenoxy)phosphoryl)acetate, KOH, THF, 73%; j. $(CH_3)_2SO_4$, K_2CO_3, acetone, 53%; k. $(Ac)_2O/Et_3N$, 94–99%.

Chart 1. Synthesis of Ethyl Cinnamate Derivatives

yield.[42] Compounds **7**–**9**, **11**, **12**, **16**–**28** were synthesized by Wittig reaction of ethyl triphenylphosphanylideneacetate [$(C_6H_5)_3P{=}CHCO_2Et$] and aromatic aldehyde in ethanol or toluene.[43] Compounds **10** and **13**–**15** were obtained by typical methyl-etherification or acetylation reaction of the corresponding hydroxyl-substituted *trans*-cinnamic acid esters (**7**–**9**). Compound **29** was synthesized by Horner–Wadsworth–Emmons (HWE) reaction of benzaldehyde with ethyl 2-(bis(2-(*tert*-butyl)phenoxy)phosphoryl)acetate in 73% yield.[44] Compound **30** was prepared by reduction of **1** with $NaBH_4$ in the presence of CuCl in 97% yield.[45] Aromatic aldehyde **1** was obtained from sesamol by the reaction of Vilsmeier–Haack formylation in 11% yield.[46] 1,3-Benzodioxole reacted with paraformaldehyde in a concentrated HCl solution to provide **2**,[47] and followed by treatment with bromine in glacial acetic acid to yield **4** in 92% yield.[48] Compounds **2** and **4** were oxidized by dimethylsulphoxide oxidation in the presence of $NaHCO_3$ to yield intermediates **3** and **5**, respectively.[49] (Chart 1).

Compounds **6**–**30** were identified by electrospray ionization (ESI)-MS, ^1H- and ^{13}C-NMR spectra. In positive or negative ESI-MS spectra, **6**–**30** showed their corresponding molecular ion peaks, quasi-molecular or pseudo-molecular ion peaks $[M+H]^+$, $[M+Na]^+$ or $[M]^-$. The NMR data were agreement with the corresponding literature data.

Pharmacology Acaricidal Activity *in Vitro* Compounds **6**–**30** were screened for the acaricidal activity *in vitro* against *P. cuniculi* according to our previously reported method.[50–52] Ivermectin, a standard acaricidal drug, was used as a reference control. The results listed in Table 1 showed that except **22**, other tested compounds showed the activity at various degrees at 1.0 mg/mL. Among them, **6**, **11**, **15**, **26**, **27** and **30** displayed the highest activity with the mite mortality of 100%, absence of significant difference from that of ivermectin (98.3%) ($p>0.05$) and the others showed low to moderate activity (6.7–62.5%). For the higher active compounds **6**, **11**, **15**, **26**, **27** and **30**, further tests were conducted at lower concentrations. The results showed that at 0.5 or 0.25 mg/mL, these compounds were significantly more active than ivermectin ($p<0.05$) with the exception of **11** (Table 1).

Acaricidal Toxicity The excellent activity of **6**, **15**, **26**, **27** and **30** in Table 1 encouraged us to further determine their acaricidal toxicity on *P. cuniculi* in order to get insight into their acaricidal potency. The assay method was the same as that described above. Ivermectin was used as a reference drug control. The activities caused by the treatment with various concentrations of the compounds for 24 h and caused by the treatment with the same concentration (4.5 μmol/mL) of the compounds for various times were shown in Figs. 1A and B, respectively. Toxicity regression equations for concentration–effect and time–effect of the compounds and their corresponding median lethal concentration values (LC_{50}) and median lethal time values (LT_{50}) were listed in Tables 2 and 3, respectively.

Figure 1A clearly showed that the activity of all the tested compounds including the positive drug ivermectin increased with increase of their respective test concentrations in a certain range of concentration. Statistical analysis further showed that at the post-treatment 24 h, each of the compounds had a significant linear correlation between the mortality rate

Table 1. The Substitution Patterns and Acaricidal Activity of the Synthesized Compounds against *P. cuniculi*

Compound	ArCH=CHCO$_2$Et		Mortality % (mean±S.D.)[a]		
	E/*Z*	Ar	1.0 mg/mL	0.5 mg/mL	0.25 mg/mL
6[c]	*E*	C_6H_5–	**100.0±0.0** a	**100.0±0.0** a	**95.0±5.5** a
7[c]	*E*	2-OH-C_6H_5–	26.7±5.2 f	ND[b]	ND
8[c]	*E*	3-OH-C_6H_5–	22.5±5.0 f	ND	ND
9[c]	*E*	4-OH-C_6H_5–	25.0±5.8 f	ND	ND
10[c]	*E*	2-OCH_3–C_6H_5–	62.5±9.6 b	ND	ND
11	*E*	3-OCH_3–C_6H_5–	**100.0±0.0** a	**35.0±5.8** c	ND
12[c]	*E*	4-OCH_3–C_6H_5–	55.0±5.5 c	ND	ND
13	*E*	2-OAc–C_6H_5–	61.7±4.1 b	ND	ND
14	*E*	3-OAc–C_6H_5–	52.5±9.6 c	ND	ND
15	*E*	4-OAc–C_6H_5–	**100.0±0.0** a	**100.0±0.0** a	**73.3±5.2** b
16	*E*	2-OH–3-OCH_3–C_6H_5–	13.3±5.2 g	ND	ND
17[c]	*E*	4-OH–3-OCH_3–C_6H_5–	13.3±5.2 g	ND	ND
18[c]	*E*	3,4-$(OCH_3)_2$–C_6H_5–	13.3±5.2 gh	ND	ND
19	*E*	2,4,5-$(OCH_3)_3$–C_6H_5–	8.3±4.1 gh	ND	ND
20[c]	*E*	3,4,5-$(OCH_3)_3$–C_6H_5–	6.7±5.2 hi	ND	ND
21	*E*	3,4-OCH_2O–C_6H_5–	21.7±4.1 f	ND	ND
22	*E*	2-OH–4,5-OCH_2O–C_6H_5–	1.7±4.1 ij	ND	ND
23	*E*	2-Br–4,5-OCH_2O–C_6H_5–	36.7±5.2 e	ND	ND
24	*E*	4-Cl–C_6H_5–	55.0±5.5 c	ND	ND
25	*E*	4-Br–C_6H_5–	50.0±8.2 c	ND	ND
26	*E*	2-NO_2–C_6H_5–	**100.0±0.0** a	**100.0±0.0** a	**100.0±0.0** a
27	*E*	3-NO_2–C_6H_5–	**100.0±0.0** a	**100.0±0.0** a	**96.7±5.2** a
28	*E*	4-NO_2–C_6H_5–	50.0±0.0 c	ND	ND
29[c]	*Z*	C_6H_5–	43.3±5.2 d	ND	ND
30[c]			**100±0.0** a	**100.0±0.0** a	**100.0±0.0** a
Ivermectin			**98.3±4.1** a	**75.0±5.8** b	**45.0±10.0** c
Control			0.0±0.0 j	0.0±0.0 d	0.0±0.0 d

a) The differences between data with the different lowercases within a column are significant ($p<0.05$). *b*) ND denotes no determination. *c*) Natural compounds.

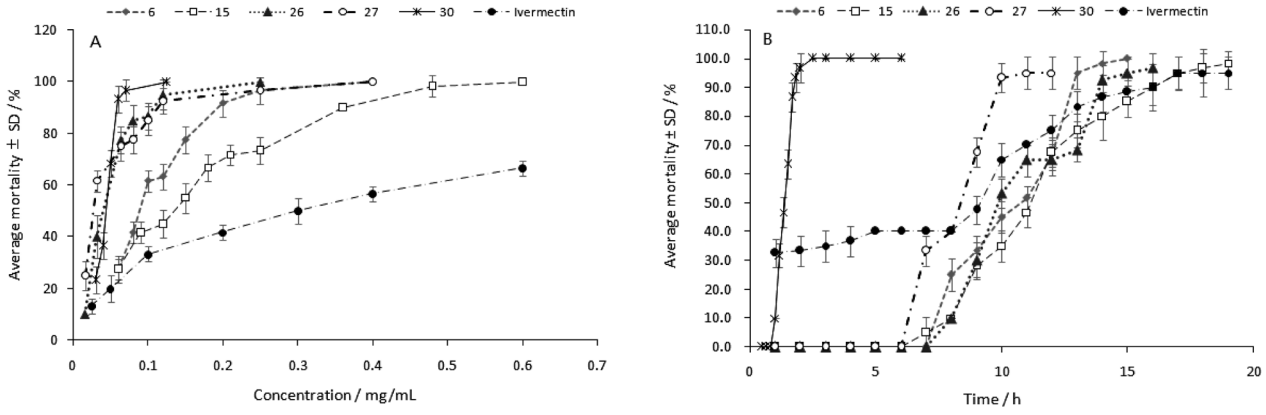


Fig. 1. Effects of Tested Concentrations (A) and Treatment Times (B) of the Compounds on the Acaricidal Activity against *P. cuniculi*

Table 2. Toxicity Regression Equations for Concentration–Effect of the Compounds and Their LC_{50} Values (24 h)

Compound	Regression equation[a]	R^2	LC_{50}		95% CI[b]	RA[c]	Linear scope (μg/mL)
			μg/mL	mmol/L			
6	$y=3.8792x-2.5675$	0.9849	89.3	0.51	86.8–91.9	2.8	60–250
15	$y=2.3377x+0.1483$	0.9679	119.0	0.51	109.4–129.3	2.1	60–360
26	$y=3.2104x-0.1148$	0.9906	39.2	0.18	37.8–40.7	6.3	16–120
27	$y=2.1307x+1.8600$	0.9550	29.8	0.13	24.8–35.8	8.3	16–120
30	$y=7.6979x-7.4278$	0.9536	41.2	0.23	39.9–42.5	6.0	30–70
Ivermectin	$y=1.3165x+1.8491$	0.9804	247.4	0.28	197.9–310.2	1.0	50–1600

a) y: Probability of average mortality; x: lg[C(μg/mL)]. *b*) 95% Confidence interval. *c*) Relative activity=LC_{50} (μg/mL) of ivermectin/LC_{50} (μg/mL) of the tested compound.

Table 3. Toxicity Regression Equations for Time–Effect of the Compounds at 4.5 μmol/mL and Their LT_{50} Values

Compound	Regression equation[a)]	R^2	LT_{50} (h)	95% CI[b)]	RA[c)]	Linear range (h)
6	$y=16.534x-11.969$	0.9022	10.6	10.5–10.7	0.84	10–14
15	$y=8.5501x-3.9043$	0.9912	11.0	10.9–11.1	0.81	8–19
26	$y=9.7377x-4.9128$	0.9489	10.4	10.2–10.7	0.86	8–16
27	$y=11.965x-5.7690$	0.9277	7.9	7.8–8.1	1.13	7–11
30	$y=10.376x-14.739$	0.9903	1.3	1.3–1.3	6.85	1–2
Ivermectin	$y=5.5047x-0.2254$	0.9840	8.9	8.8–9.0	1.00	8–17

a) *y*: Probability of average mortality. For **6**, **15**, **26** and **27**, $x=\lg[t(\text{h})]$; for **30**, $x=\lg[t(\text{min})]$. *b*) 95% Confidence interval. *c*) Relative activity=LT_{50} of ivermectin/LT_{50} of the tested compound.

probabilities and lg[concentration (μg/mL)] values in different concentration ranges ($R^2>0.95$) (Table 2). As expected, **6**, **15**, **26**, **27** and **30** displayed the smaller LC_{50} values of 29.8–119.0 μg/mL than ivermectin (LC_{50}=247.4 μg/mL) and their relative activities (RA) reached up to 2.8-, 2.1-, 6.3-, 8.3- and 6.0-fold the activity of ivermectin (Table 2). The results above were agreement with that observed in the activity screening experiment (Table 1). Among these compounds, **27** showed the highest activity with a LC_{50} value of 29.8 μg/mL followed by **26** and **30** (LC_{50}=39.2, 41.2 μg/mL). In addition, comparison of the change trend of the various curves in Fig. 1A showed that various compounds had different activity sensitivity to the change of test concentration with the order of **30**>**27**≈**26**>**6**>**15**>ivermectin.

Figure 1B showed that the activity of each compound at 4.5 μmol/mL exhibited treatment-time-dependent effects in a certain time range. Linear regress analysis showed that each of the compounds showed a significant linear correlation between the probability values of mite mortality and lg[treatment time (h or min)] values in a specific time range ($R^2>0.90$) (Table 3). Compared with ivermectin with a LT_{50} value of 8.9 h, **27** and **30** (LT_{50}=7.9, 1.3 h) showed the higher activity whereas **6**, **15** and **26** (LT_{50}=10.6, 11.0, 10.4 h) showed the slightly lower activity. Especially, the relative activity of **30** attained 6.85-fold of that of ivermectin. On the other hand, the change trend of the various curves in Fig. 1B presented that the activity susceptibilities of the various compounds to the treatment time were as the following order: **30**>**27**>**26**≈**6**>**15**>ivermectin.

SAR The present research showed that almost all the cinnamate derivatives have the acaricidal activity at a certain degree (Table 1). Comparison of the activity and structure of the various compounds revealed that a substituent on the benzene ring and its substitution site can significantly influence the activity of ethyl cinnamate. Compared with an unsubstituted compound **6** (LC_{50}=89.3 μg/mL), the presence of *o*-NO_2 or *m*-NO_2 (**26** and **27**) led to a significant improvement of the activity (LC_{50}=39.2, 29.8 μg/mL) whereas *p*-NO_2 derivative (**28**) showed the lower activity (Table 1). Unlike the situation of nitro group, the introduction of a hydroxyl, methoxyl or acetoxyl to any site on the benzene ring (**7**–**15**) led to reduce the activity. Meanwhile, the activities of methoxyl-substituted compounds (**18**–**20**) reduced with increasing the number of substituted methoxy groups. In addition, the presence of methylenedioxy, bromo or chloro groups at some sites also led to reduction of the activity, such as **21**–**25**.

Compound **6** showed the higher activity than its configurational isomer **29** (Table 1), indicating that the *E* configuration of cinnamic acid esters is more beneficial for the activity than the corresponding *Z* configuration. Nevertheless, the presence of the carbon–carbon double bond in the acrylic ester moiety was not essential to improve the activity of cinnamic acid esters, which was evidenced by the fact that **6** (LC_{50}=89.3 μg/mL, LT_{50}=10.6 h) was less active than its dihydro derivative **30** (LC_{50}=41.2 μg/mL, LT_{50}=1.3 h). Although the similar case was also found for HIV-1 integrase activity of cinnamic acid esters,[53] the double bond was thought to be crucial for other bioactivities such as leishmanicidal and cytotoxic,[38] antituberculosis (TB)[22,24] and anti-candida albicans biofilm.[16] The leishmanicidal and cytotoxic action of cinnamic acid esters had been explained as a Michael addition mechanism,[38] in which cinnamic acid esters as one type of α,β-unsaturated carbonyl compounds were considered to have a conjugated addition reaction with nucleophilic groups in biomolecules of the natural receptors. This mechanism was also reported for other α,β-unsaturated carbonyl compounds such as lactones, chalcones and coumarins.[54–56] Obviously, the present results strongly suggest that the acaricidal action of cinnamic acid esters might not be Michael addition mechanism and different action mechanisms may be responsible for the different bioactivity of cinnamic acid esters.

Furthermore, the conjecture above was also supported by the fact that the effects of substituents on the benzene on the acaricidal activity of cinnamic acid esters and other bioactivities are different. The present research showed that the introduction of a hydroxyl, methoxyl or acetoxyl on the benzene ring did not improve the acaricidal activity. But in the leishmanicidal activity and cytotoxicity of cinnamic acid esters,[38] chalcones[57] and coumarins,[58] the presence of hydroxyl or methoxyl groups led to enhancement of the activities.

From the point of view of median lethal mass concentration values (μg/mL), compounds **6**, **15**, **26**, **27** and **30** should theoretically have a great advantage in practice application over ivermectin, due to their lower LC_{50} values (μg/mL) than ivermectin (Table 2). However, as far as SAR analysis is concerned, researchers prefer to compare median lethal molar concentration values (mol/L) of various compounds. Though **6** and **15** had the different median lethal mass concentration values (μg/mL), lower than that of ivermectin, they had approximately the same median lethal molar concentration values (mol/L), larger than that ivermectin (Table 2). Therefore, for single molecule, **6** and **15** had the same acaricidal activity, indicating that the presence of 4-acetyl hardly influenced the activity (Fig. 2).

As is shown in Table 3, at the same molar concentration (4.5 μmol/mL), **6**, **15**, **26**, **27** and **30** showed lower or slightly higher LT_{50} values (1.3–11.0 h) than ivermectin (LT_{50}=8.9 h). However, it was worth mentioning that the molecular weight of ivermectin (MW=875) is much larger than that of **6**, **15**,

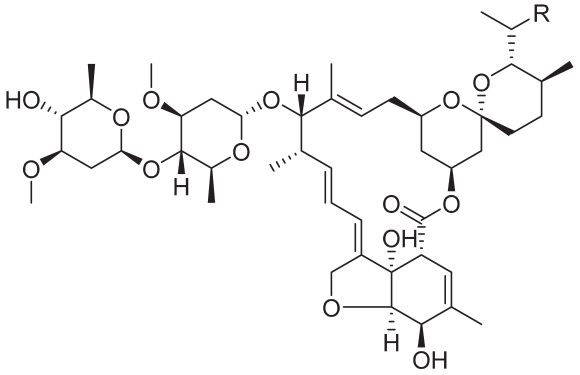


Fig. 2. The Structure of Ivermectin (22,23-Dihydroavermectin B_1 Consisting of B_{1a} and B_{1b})

26, **27** and **30** (MW=176–234). At the test concentration of 4.5 μmol/mL, the mass concentration of ivermectin (3.94 mg/mL) was 3.6–5.0 times of that of **6**, **15**, **26** and **27** (0.8–1.1 mg/mL). Based on the results that at the same test molar concentration, **6**, **15**, **26**, **27** and **30** possessed lower or slightly higher LT_{50} values (1.3–11.0) than ivermectin (LT_{50}=8.9 h), it was deduced that **6**, **15**, **26** and **27** probably have much lower LT_{50} values than ivermectin if the same test mass concentration was used, which may be evidenced by the results in Fig. 1A to some degree.

The present research strongly suggests that further research should be necessary on the acaricidal mechanism of cinnamic acid esters as well as more diverse structural modification including cinnamamides, 3-aryl fatty acid esters or amides and even 3-aryl aliphatic ketones. At present, these works are partly underway in our lab.

Conclusion

In conclusion, the present study reported the synthesis of a series of ethyl cinnamate derivatives and the acaricidal activity *in vitro* against *Psoroptes cuniculi*, a mange mite. Furthermore, the preliminary SAR was discussed. Almost all the compounds were found to have the activity in varying degrees at 1.0 mg/mL for post-treatment 24 h and of which 5 showed much lower LC_{50} values and slightly lower or higher LT_{50} values than a standard drug ivermectin. SAR showed that the presence of *o*-NO_2 or *m*-NO_2 on the benzene ring led to significant improvement of the activity. In contrast, a hydroxy, methoxy, acetoxy, methylenedioxy, bromo or chloro group led to activity reduction. The *E*-isomer was found to be more beneficial for improving the activity than the corresponding *Z*-isomer. Nevertheless, the carbon–carbon double bond in the acrylic ester moiety was proven not to be essential to improve the activity of cinnamic acid esters. Thus, the present study strongly suggests that cinnamic acid esters and their dihydro derivatives are promising candidates or lead compounds for the development of novel drugs for the effective control of animal or human acariasis.

Experimental

Materials Ivermectin (≥91% 22,23-dihydroavermectin B_1 consisting of 95% avermectin B_{1a} and 5% avermectin B_{1b}) was purchased from Sigma-Aldrich Trading Co., Ltd., Shanghai, China. Other chemicals used in the present study were purchased from J&K Chemical Ltd., Beijing, China and used without further purification.

Apparatus Melting points (mp) were determined on an XT-4 micro-melting point apparatus and uncorrected. ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker AVANCE III operating at 500 or 400 MHz, respectively and using tetramethyl silane (TMS) as an internal standard. ESI-MS was measured on a Trace mass spectrometer.

Synthesis of Compound 6 According to the literature's method,[42] compound **6** was obtained by the reaction of cinnamic acid (1.48 g, 10 mmol) with absolute ethanol (15 mL) at 0°C to room temperature by dropwise addition of thionyl chloride (3.57 g, 30 mmol).

(*E*)-Ethyl Cinnamate (**6**): Colorless liquid in 95% yield. The data of ^{1}H- and ^{13}C-NMR were consistent with those in the literature.[59] Positive ESI-MS *m/z*: 177 $[M+H]^+$.

Synthesis of Compounds 7–9, 11, 12 and 16–28 Ethyl triphenylphosphanylideneacetate ($(C_6H_5)_3P=CHCO_2Et$) (4.2 g, 12 mmol) reacted with aromatic aldehyde (10 mmol) in 50 mL ethanol at reflux for 1–4 h (compds. **7**, **11**, **12**, **16**–**28**) or 50 mL toluene at reflux for 0.5 h (compds. **8** and **9**) to yield the desired compounds according to the reported method[43] with slight modification. After removal of the solvent, the resulting residue was subjected to a short silica gel column chromatography (ϕ40 mm×*L* 40 mm) using petroleum ether–ethyl acetate as eluent to remove polar triphenylphosphine oxide. For the preparation of compounds **8**, **9**, **19**, **20, 22**, **23**, **26**–**28**, the obtained crude products were directly recrystallized in petroleum ether–ethyl acetate (**8**, **9**, **19**, **20**, **23**, **26**–**28**) or petroleum ether–ethanol (**22**); for the purification of the target compounds **7**, **11**, **12**, **16**–**18**, **21**, **24** and **25**, the obtained crude products were re-chromatographed over silica gel (ϕ26 mm×*L* 140 mm or ϕ40 mm×*L* 200 mm) using petroleum ether–ethyl acetate (**7**, **16**, **17**, **21**) or petroleum ether–ethyl ether (**11**, **12**, **18**, **24**, **25**) as eluent.

(*E*)-Ethyl 2-Hydroxycinnamate (**7**): White crystal in 73% yield, mp 80–81°C (lit.[60] 83–86°C). The data of ^{1}H- and ^{13}C-NMR were consistent with those in the literature.[61] Positive ESI-MS *m/z*: 193 $[M+H]^+$.

(*E*)-Ethyl 3-Hydroxycinnamate (**8**): White lamellar crystal in 64% yield, mp 65–66°C (lit.[62] 67.7–68.7°C). ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.64 (1H, d, *J*=16.0 Hz), 7.24 (1H, t, *J*=8.1 Hz), 7.06–7.07 (2H, m), 6.91–6.93 (1H, m), 6.83 (1H, br s, OH), 6.40 (1H, d, *J*=16.0 Hz), 4.28 (2H, q, *J*=7.1 Hz), 1.34 (3H, t, *J*=7.1 Hz). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 167.9, 156.5, 145.2, 135.7, 130.1, 120.6, 118.1, 117.8, 114.7, 61.0, 14.3. Positive ESI-MS *m/z*: 193 $[M+H]^+$.

(*E*)-Ethyl 4-Hydroxycinnamate (**9**): White rod-like crystal in 78% yield, mp 74–75°C (lit.[63] 73°C). The data of ^{1}H- and ^{13}C-NMR were consistent with those in the literature.[64] Positive ESI-MS *m/z*: 193 $[M+H]^+$.

(*E*)-Ethyl 3-Methoxycinnamate (**11**): Yellow oil[65] in 78% yield. The data of ^{1}H-NMR were consistent with those in the literature.[66] ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 166.9, 159.9, 144.5, 135.9, 129.9, 120.8, 118.6, 116.1, 112.9, 60.5, 55.3, 14.3. Positive ESI-MS *m/z*: 207 $[M+H]^+$.

(*E*)-Ethyl 4-Methoxycinnamate (**12**): Faint yellow powder in 62% yield, mp 45–46°C (lit.[67] 48–50°C). The data of ^{1}H- and ^{13}C-NMR were consistent with those in the literature.[68] Positive ESI-MS *m/z*: 207 $[M+H]^+$.

(*E*)-Ethyl 2-Hydroxy-3-methoxycinnamate (**16**): White crystal in 92% yield, mp 59–60°C (lit.[69] 68–69°C). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.94 (1H, d, J=16.2 Hz), 7.08 (1H, dd, J=6.9, 2.4 Hz), 6.81–6.87 (2H, m), 6.60 (1H, d, J=16.2 Hz), 6.20 (1H, s, –OH), 4.26 (2H, q, J=7.1 Hz), 3.90 (3H, s), 1.34 (3H, t, J=7.1 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 167.5, 146.8, 145.4, 139.5, 120.93, 120.89, 119.6, 119.3, 111.7, 60.3, 56.2, 14.4. Negative ESI-MS *m/z*: 221 $[M-H]^-$.

(*E*)-Ethyl 4-Hydroxy-3-methoxycinnamate (**17**): White powder in 55% yield, mp 42–43°C (lit.[70] 57.3–58.0°C). The data of ^{1}H- and ^{13}C-NMR were consistent with those in the literature.[71] Negative ESI-MS *m/z*: 221 $[M-H]^-$.

(*E*)-Ethyl 3,4-Dimethoxylcinnamate (**18**): Faint yellow powder in 81% yield, mp 52–53°C (lit.[72] 49–51°C). The data of ^{1}H- and ^{13}C-NMR were consistent with those in the literature.[73] Positive ESI-MS *m/z*: 237 $[M+H]^+$.

(*E*)-Ethyl 2,4,5-Trimethoxylcinnamate (**19**): Faint yellow crystal in 60% yield, mp 63–64°C (lit.[74] 68–69°C). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.97 (1H, d, J=16.0 Hz), 7.01 (1H, s), 6.50 (1H, s), 6.37 (1H, d, J=16.0 Hz), 4.28 (2H, q, J=7.1 Hz), 3.93 (3H, s), 3.88 (3H, s), 3.86 (3H, s), 1.34 (3H, t, J=7.1 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 167.3, 153.3, 151.5, 142.7, 139.0, 115.3, 114.4, 110.2, 96.3, 59.7, 55.9, 55.8, 55.5, 13.9. Positive ESI-MS *m/z*: 267 $[M+H]^+$.

(*E*)-Ethyl 3,4,5-Trimethoxylcinnamate (**20**): White needle crystal in 42% yield, mp 66–67°C (lit.[75] 68–69.5°C). The data of ^{1}H-NMR were consistent with those in the literature.[75] ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 167.0, 153.4, 144.6, 140.0, 130.0, 117.5, 105.2, 61.0, 60.5, 56.1, 14.3. Positive ESI-MS *m/z*: 267 $[M+H]^+$.

(*E*)-Ethyl 3,4-Methylenedioxycinnamate (**21**): White crystal in 78% yield, mp 59–60°C (lit.[76] 68–70°C). The data of ^{1}H- and ^{13}C-NMR were consistent with those in the literature.[76] Positive ESI-MS *m/z*: 221 $[M+H]^+$.

(*E*)-Ethyl 2-Hydroxy-4,5-methylenedioxycinnamate (**22**): Bright yellow crystal in 76% yield, mp 149–150°C (lit.[43] 149–150°C). The data of ^{1}H- and ^{13}C-NMR were agreement with those in the literature.[43] Positive ESI-MS *m/z*: 237 $[M+H]^+$.

(*E*)-Ethyl 2-Bromo-4,5-methylenedioxycinnamate (**23**): Faint yellow needle crystal in 58% yield, mp 113–114°C (lit.[77] mp 78–80°C). The data of ^{1}H- and ^{13}C-NMR were consistent with those in the literature.[77] Positive ESI-MS *m/z*: 299 $[M+H]^+$.

(*E*)-Ethyl 4-Chlorocinnamate (**24**): Yellow liquid[68] in 83% yield. The data of ^{1}H- and ^{13}C-NMR were agreement with those in the literature.[68] Positive ESI-MS *m/z*: 211 $[M+H]^+$.

(*E*)-Ethyl 4-Bromocinnamate (**25**): Yellow liquid in 87% yield. The data of ^{1}H- and ^{13}C-NMR were agreement with those in the literature.[78] Positive ESI-MS *m/z*: 279 $[M+Na]^+$.

(*E*)-Ethyl 2-Nitrocinnamate (**26**): Faint yellow crystal in 52% yield, mp 38–39°C (lit.[79] 42°C). The data of ^{1}H-NMR were agreement with those in the literature.[66] ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 165.8, 148.4, 139.8, 133.5, 130.7, 130.3, 129.1, 124.9, 123.4, 60.9, 14.3. Negative ESI-MS *m/z*: 221 $[M]^-$.

(*E*)-Ethyl 3-Nitrocinnamate (**27**): Faint yellow needle crystal in 57% yield, mp 73–74°C (lit.[80] 74–75°C). The data of ^{1}H- and ^{13}C-NMR were agreement with those in the literature.[80] Negative ESI-MS *m/z*: 221 $[M]^-$.

(*E*)-Ethyl 4-Nitrocinnamate (**28**): Yellow rod-like crystal in 64% yield, mp 135–136°C (lit.[67] 138–140°C). The data of ^{1}H- and ^{13}C-NMR were agreement with those in the literature.[81] Negative ESI-MS *m/z*: 221 $[M]^-$.

Synthesis of Compound 10 According to a typical methoxylation method of phenols, compound **7** (0.58 g, 3.0 mmol) reacted with dimethyl sulfate (0.38 g, 3.0 mmol) in 20 mL acetone in the presence of potassium carbonate (0.5 g, 3.6 mmol) to yield compound **10**.

(*E*)-Ethyl 2-Methoxycinnamate (**10**): Faint yellow oil in 53% yield (lit.[65] mp 33–34°C). The data of ^{1}H-NMR were agreement with those in the literature.[66] ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 167.6, 158.4, 140.0, 131.4, 128.9, 123.5, 120.7, 118.8, 111.1, 60.4, 55.5, 14.4. Positive ESI-MS *m/z*: 207 $[M+H]^+$.

Synthesis of Compounds 13–15 General Procedure According to a typical acetylation method of phenols, the solution of compounds **7**–**9** (0.4 g, 2.1 mmol) and acetic anhydride (0.6 g, 6.2 mmol) in 20 mL triethylamine was stirred for 1 h at room temperature to provide the desired compounds (**13**–**15**).

(*E*)-Ethyl 2-Acetoxycinnamate (**13**): Faint yellow oil in 99% yield. The data of ^{1}H- and ^{13}C-NMR were consistent with those in the literature.[82] Positive ESI-MS *m/z*: 235 $[M+H]^+$.

(*E*)-Ethyl 3-Acetoxycinnamate (**14**)[83]: Faint yellow oil in 94% yield. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.65 (1H, d, J=16.0 Hz), 7.37–7.41 (2H, m), 7.25–7.26 (1H, m), 7.10–7.12 (1H, m), 6.42 (1H, d, J=16.0 Hz), 4.26 (2H, q, J=7.1 Hz), 2.31 (3H, s), 1.33 (3H, t, J=7.1 Hz). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 169.3, 166.7, 151.1, 143.4, 136.1, 129.9, 125.6, 123.4, 120.9, 119.4, 60.6, 21.1, 14.3. Positive ESI-MS *m/z*: 235 $[M+H]^+$.

(*E*)-Ethyl 4-Acetoxycinnamate (**15**): White powder in 98% yield, mp 37–38°C (lit.[84] mp 40–42°C). The data of ^{1}H- and ^{13}C-NMR were consistent with those in the literature.[84] Positive ESI-MS *m/z*: 235 $[M+H]^+$.

Synthesis of Compound 29 According to the literature method,[44] compound **29** was obtained by HWE reaction of ethyl 2-(bis(2-(*tert*-butyl)phenoxy)phosphoryl)acetate (0.476 g, 1.1 mmol) with benzaldehyde (0.106 g, 1 mmol) 15 mL anhydrous tetrahydrofuran in the presence of KOH (0.09 g, 1 mmol) at 0°C for 2 h.

(*Z*)-Ethyl Cinnamate (**29**): Colorless liquid in 73% yield. The ^{1}H-NMR data were consistence with those in the literature.[59]

Synthesis of Compound 30 According to the literature method,[45] compound **30** was prepared by reduction of compound **6** (0.88 g, 5 mmol) with borohydride (0.19 g, 5 mmol) in 20 mL methanol in the presence of cuprous chloride (0.29 g, 3 mmol).

Ethyl 3-Phenylpropionate (**30**): Colorless liquid in 95% yield. The data of ^{1}H- and ^{13}C-NMR were agreement with those in the literature.[85]

Pharmacology *In Vitro* Acaricidal Activity Assay *In vitro* acaricidal activity of **6**–**30** was performed according to our previously reported method.[50–52] Ivermectin, a standard acaricidal drug, was used as a reference control. All the tested compounds were dissolved in a mixed solvent of dimethyl sulfoxide (DMSO), Tween-80 and normal saline (1 : 1 : 8, v/v/v) to prepare the test solution with the concentration of 1, 0.5 or 0.25 mg/mL. *Psoroptes cuniculi* adult mites of both sexes isolated from naturally infected rabbits were used as the tested objects. The scabs and the cerumen, collected from the infected ears, were observed by means of a stereoscopic microscope to isolate adult mites of both sexes. Mites were placed in 24-

well flat-bottomed cell culture plates (10 adult mites per each well) and followed by addition of 0.6 mL of the tested solution into each well. Each 20 mites in 2 wells were set as one test and three replicates were made for each concentration. The same solution without the tested compound was used as an untreated control. Ivermectin in the same solvent represented the treated control.

All the plates were placed in separate humidity chambers in saturated humidity conditions at 28°C. After 24 h each plate was observed under a stereomicroscope for 5 min. When the persistent immobile mites were stimulated with a needle, lack of reaction was considered as the indication of death. Mortality was calculated as the following formula and expressed as means±standard deviation (S.D.):

$$\text{Mortality (\%)} = \frac{\text{Number of death mites}}{\text{Number of the tested mites}} \times 100$$

Acaricidal Toxicity Assay Based on the above results of acaricidal screening, the most effective compounds **6**, **15**, **26**, **27** and **30** were further subjected to acaricidal toxicity evaluations on *P. cuniculi* including the effects of tested concentration and treatment time on the activity. Ivermectin was used as a reference drug control.

A 2.0 mg/mL stock solution of the tested compound was prepared in the same solvent as described above, and then diluted with the same mixed solvent to obtain a series of concentrations. The acaricidal activity for each concentration was tested according to the same procedure as described above. The mortality of mites for each test was calculated and then corrected by applying Abbott's formula:

$$\text{Corrected mortality (\%)} = \frac{\text{test mortality (\%)} - \text{control mortality (\%)}}{100 - \text{control mortality (\%)}} \times 100$$

The tested compounds mentioned above at 4.5 μmol/mL in the same mixed solvent as described above were prepared to determine LT_{50} values. The acaricidal activity of each tested compound was assayed according to the method described above. The mites in each well were observed under a stereomicroscope every 10 min or 1.0 h and the mortality and corrected mortality of each test in each set time were calculated. The tested compound was performed in triplicate. The corrected mortality of each test was expressed as means±S.D.

The probit value of the corrected mortality for each tested concentration and the corresponding lg[concentration (μg/mL)] were used to establish toxicity regression equation for concentration–effect by the linear least-square fitting method. Toxicity regression equation for time–effect was established between the probit value of the corrected mortality for each set treatment time and the corresponding lg [treatment time (h or min)] value. The LC_{50} or LT_{50} value of each compound and their confidence intervals at 95% probability were calculated from the corresponding toxicity regression equation.

Statistic Analysis SPSS 17.0 statistical software was used to analyze the data and establish toxicity regression equations. Duncan multiple comparison test was performed on the data to evaluate significant difference between the activities of various compounds at the same concentration.

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Conflict of Interest The authors declare no conflict of interest.

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