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Synthesis and fungicidal activities of novel benzothiophene-substituted oxime ether strobilurins

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ABSTRACT

Twenty-one novel benzothiophene-substituted oxime ether strobilurins, which employed a benzothiophene group to stabilise the *E*-styryl group in Enoxastrobin (an unsaturated oxime strobilurin fungicide developed by Shenyang Research Institute of Chemical Industry, China) were designed and synthesised. The biological assay indicated that most compounds exhibited good or excellent fungicidal activities, especially against *Colletotrichum lagenarium* and *Puccinia sorghi* Schw. In addition, methyl 3-methoxypropenoate oxime ethers and *N*-methoxy-carbamic acid methyl esters exhibited good in vivo fungicidal activities against *Erysiphe graminis*, *Colletotrichum lagenarium* and *Puccinia sorghi* Schw. under the tested concentrations. Notably, (*E*,*E*)-methyl 3-methoxy-2-(2-((((6-chloro-1-(1*H*-benzo[*b*]thien-2-yl)ethylidene)amino)oxy)methyl)phenyl)propenoate (**5E**) exhibited more potent in vivo fungicidal activities against nearly all of the tested fungi at a concentration of 0.39 mg/L compared to Enoxastrobin.

Strobilurins are naturally occurring derivatives of β-methoxyacrylic acid that comprise an important class of agricultural fungicides.[1–4] However, these compounds are natural, and they could not be used directly due to insufficient photochemical stability and volatility.[2,5] To date, several chemists have published synthetic analogues of strobilurin **A** (Fig. 1) to stabilise the triene structure of the compound.[6–14]

Compounds **I** (Fig. 1), which were discovered by the Rohm and Haas Company [the 4-Cl-substituted derivatives of compounds **I** were developed by Shenyang Research Institute of Chemical Industry and named Enoxastrobin (Fig. 1)[10]], contain an unsaturated oxime ether group and exhibit effective fungicidal activities.[7] In addition, novel arylcyclopropyl oxime ether compounds **II** (Fig. 1), which replace the *E*-styryl group in compounds **I** with a *trans*-arylcyclopropyl group, have been reported. These compounds exhibit excellent fungicidal activities.[8] In our previous study, we synthesised a series of novel indene–substituted oxime ethers **III** (Fig. 1) to study the structure–activity relationships of this type of compound.[12,15] A benzopentatomic ring structure was used to stabilise the *E*-styryl group in Enoxastrobin. Most of the indene–substituted oxime ethers (**III**) exhibited effective fungicidal activity. In addition, the fungicidal activities of some compounds (**III**) were better than those of Enoxastrobin.

Many heterocyclic compounds have shown good insecticidal or fungicidal activities, increasing their importance in pesticide discovery.[16–21] The heterocyclic scaffold of a crop protection agent often has a positive effect on its synthetic accessibility and its physicochemical properties, driving values, such as lipophilicity and solubility toward the optimal balanced range for uptake and bioavailability.[16] Heterocycles are deemed to be perfect bioisosteres of other carba- or heterocyclic rings as well as of several different functional groups which deliver equal or even better biological efficacy through their similarity in structural shape and electronic distribution.[16,20] In addition, the substitution of a heteroaryl group (i.e., pyridine or furane) with one of the aryl residues of the compound results in increased biological activity.[21] More importantly, environmental compatibility of the synthesised organic compounds is enhanced when heteroatoms are introduced into the carba-rings.[16,19,20]

Based on these facts, a series of novel benzothiophene-substituted oxime ethers **5** (Fig. 1) utilising a benzothiophene group as a bioisostere to replace the *E*-styryl group in Enoxastrobin was synthesised in this Letter. The target compounds (**5**) were predicted to retain or further enhance their biological activity and simultaneously improve their environmental compatibility. The structure–activity relationship of this type of compound was also studied. The biological assay indicated that most compounds (**5**) maintained or enhanced their fungicidal activities compared to Enoxastrobin.

The synthetic route for the target compounds is outlined in Scheme 1, and the reaction yields were not optimised.

The 2-(ethylthio)-benzaldehyde intermediates (**2**) were prepared according to a previously published protocol.[22] the

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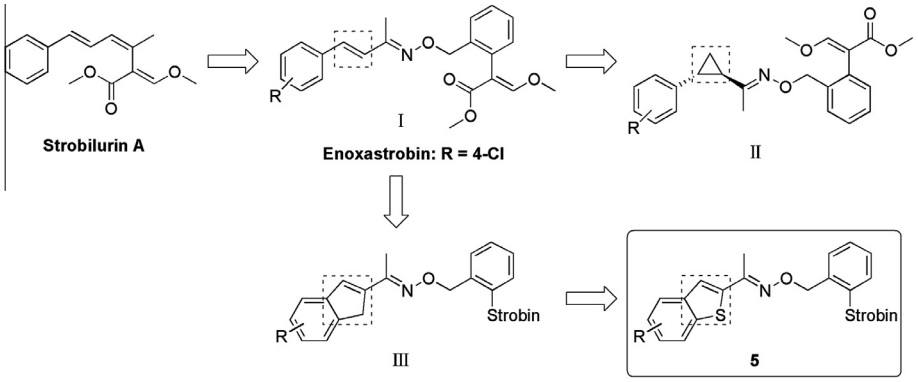


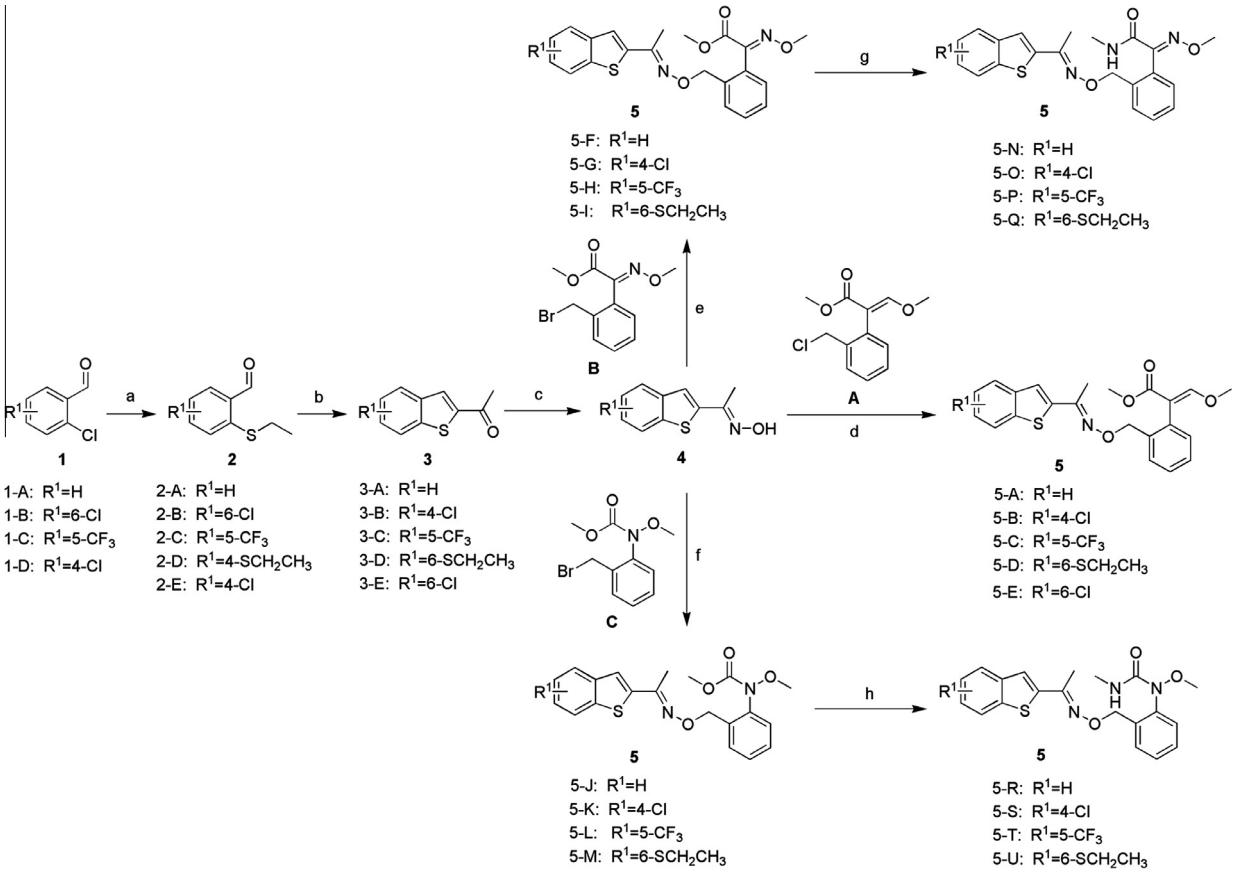
Figure 1. Structure of strobilurin **A** and its analogues.

2-chlorobenzaldehydes (**1**) were reacted with 1.4 equiv of ethanethiol in the presence of 1.4 equiv of sodium hydroxide and 0.03 equiv of tetrabutylammonium bromide at 82 °C for 4.0–6.0 h to afford 2-(ethylthio)-benzaldehydes (**2A**, **2B**, **2C** and **2E**). 2,4-Dichlorobenzaldehyde was reacted with 2.8 equiv of ethanethiol in the presence of 2.8 equiv of sodium hydroxide and 0.06 equiv of tetrabutylammonium bromide at 82 °C for 2.5 h to yield 2,4-bis(ethylthio)benzaldehyde (**2D**). When 2,4-dichlorobenzaldehyde (R^1 = 4-Cl) was used to synthesis **2E**, significant byproduct, presumably from the reaction of 4-Cl in 2,4-dichlorobenzaldehyde with ethanethiol, made isolation of the product difficult. Due to the low yielding nature of this reaction and difficulties with purification, only one derivative where R^1 = 6-Cl (**5E**) were synthesized.

Second, according to the literature,[22] the 2-(ethylthio)-benzaldehydes (**2**) were reacted with 1.25 equiv of 1-chloropropan-2-one in the presence of 1.25 equiv of potassium carbonate at 59 °C to afford 1-(benzo[*b*]thiophen-2-yl)ethanones (**3**) in good yields.

Then, according to a previously described method,[23] the 1-(benzo[*b*]thiophen-2-yl)ethanones (**3**) were reacted with 1.5 equiv of hydroxylamine hydrochloride and 1.5 equiv of sodium acetate trihydrate in the presence of a 2:1 (v/v) mixture of ethanol and water under reflux to produce (*E*)-1-(1*H*-benzo[*b*]thien-2-yl)ethanoneoximes (**4**) in high yields.

Next, the target compounds (**5A**–**M**) were obtained by reaction of ethanone oximes (**4**) with (*E*)-methyl 2-(2-(chloromethyl)phenyl)-3-methoxypropenoate (**A**), (*E*)-methyl 2-(2-(bromomethyl)



Scheme 1. General synthetic route for the target compounds **5**. Reagents and conditions: (a) NaOH, H_2O, tetrabutylammonium bromide, ethanethiol, 82 °C, 4.0–6.0 h; (b) 1-chloropropan-2-one, CaO, acetone, 59 °C, 10.0–14.0 h; (c) hydroxylamine hydrochloride, sodium acetate, 2:1 (v/v) mixture of ethanol and H_2O, reflux, 0.5–9.5 h; (d–f) K_2CO_3, anhydrous acetonitrile, reflux, 5.0–14.5 h; (g and h) CH_3NH_2, methanol, reflux, 0.5–18.0 h.

phenyl)-2-methoxyiminoacetate (**B**) or methyl (2-(bromomethyl)-phenyl)methoxycarbamate (**C**) in the presence of a base and solvent according to a literature protocol.[15,21] The target compounds (**5N–Q** and **5R–U**) were produced by ammonolysis of the corresponding target compounds methyl α-(methoxy-imino)benzeneacetate oxime ethers (**5F–I)** and *N*-methoxy-carbamic acid methyl esters (**5J–M**) according to a literature protocol.[24] The structures of the desired compounds were confirmed by ^{1}H NMR, ^{13}C NMR and HRMS.

Evaluation of the biological activities of compounds **5** was performed according to previously published protocols.[12,25–31]

The results of fungicidal activity are listed in Tables 1 and 2, where the inhibition percentage was expressed as the mean of the values obtained in three independent experiments. The biological data were reported as a range from 0% (indicates no control) to 100% (complete control). To determine the fungicidal potency of the target compounds, a commercial oxime ether fungicide (i.e., Enoxastrobin) was used as the standard.

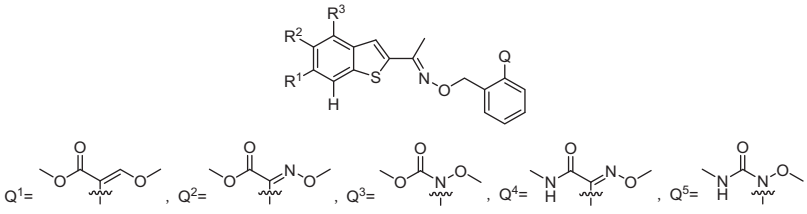
The in vitro fungicidal activity results for compounds **5** against *Pyricularia oryzae* and *Botrytis cinerea* at a concentration of 6.25 mg/L are listed in Table 1. The results of the preliminary bioassays were compared to those of Enoxastrobin. Compounds **5** exhibited potent fungicidal activities against the tested fungi. All of the compounds were more potent or exhibited a similar potency for in vitro fungicidal activities against *P. oryzae* and *B. cinerea* compared to Enoxastrobin. Compounds **5** exhibited 100% growth inhibition against *B. cinerea.*

Compounds **5** were tested in vivo against *Erysiphe graminis*, *Colletotrichum lagenarium*, *Psilocybe cubensis* and *Puccinia sorghi* Schw. at 100 mg/L (Table 1). Most of the compounds exhibited effective fungicidal activities. Some compounds exhibited better fungicidal activities against *E. graminis*, *C. lagenarium* and *P. sorghi* Schw. but lower activities against *P. cubensis* compared to Enoxastrobin. In addition, all of the synthesised methyl 3-methoxypropenoate oxime ethers (**5A–E**) and *N*-methoxy-carbamic acid methyl esters (**5J–M**) exhibited substantial fungicidal activities against *E. graminis*, *C. lagenarium* and *P. sorghi* Schw.

Compounds **5A–E** and **5J–M** were tested in vivo against *E. graminis*, *C. lagenarium* and *P. sorghi* Schw. at lower concentrations (Table 2). The results indicate that **5A–E** and **5J–M** exhibited good fungicidal activities against *E. graminis*, *C. lagenarium* and *P. sorghi* Schw. at a concentration of 1.56 mg/L. Especially, the 6-chlorobenzothiophene-substituted compound (**5E**) was the most promising candidate for further study because it exhibited more potent fungicidal activities against nearly all of the tested fungi at 0.39 mg/L compared to Enoxastrobin and it owned a broader spectrum of fungicidal activities.

In summary, a series of new benzothiophene-substituted oxime ether strobilurins (**5**) were designed and synthesised by modifying the side chain of an unsaturated oxime ether strobilurin fungicide (i.e., Enoxastrobin). The biological assay results indicated that most compounds maintained or enhanced their fungicidal activities, especially against *C. lagenarium* and *P. sorghi* Schw. In addition, methyl 3-methoxypropenoate oxime ethers (**5A–E**) and *N*-methoxy-carbamic acid methyl esters (**5J–M**) exhibited good in vivo fungicidal activities against *E. graminis*, *C. lagenarium* and *P. sorghi* Schw. Notably, **5E** exhibited more potent fungicidal activities

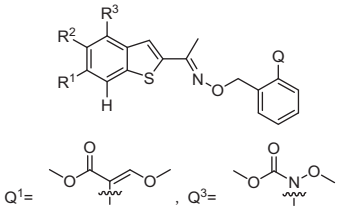
Table 1
Chemical structures and fungicidal activity of target compounds **5** (inhibition %)



No.	Substituents				Testing concentration (mg/L)					
					6.25 mg/L		100 mg/L			
	R^1	R^2	R^3	Q	*P. oryzae*	*B. cinerea*	*E. graminis*	*C. lagenarium*	*P. cubensis*	*P. sorghi* Schw.
5A	H	H	H	Q^1	50	100	100	100*	95	100*
5B	H	H	Cl	Q^1	50	100	90	100	90	100
5C	H	CF_3	H	Q^1	50	100	100	95	0	80
5D	SCH_2CH_3	H	H	Q^1	50	100	100	100*	0	80
5E	Cl	H	H	Q^1	50	100	90	100	95	100
5F	H	H	H	Q^2	50	100	100	100*	95	90
5G	H	H	Cl	Q^2	50	100	0	0	0	0
5H	H	CF_3	H	Q^2	50	100	90	70	0	70
5I	SCH_2CH_3	H	H	Q^2	50	100	0	50	0	80
5J	H	H	H	Q^3	80	100	100	100	0	90
5K	H	H	Cl	Q^3	50	100	100	100	0	100*
5L	H	CF_3	H	Q^3	50	100	100	80	0	80
5M	SCH_2CH_3	H	H	Q^3	50	100	100	95	0	100
5N	H	H	H	Q^4	50	100	0	0	0	0
5O	H	H	Cl	Q^4	50	100	0	0	0	0
5P	H	CF_3	H	Q^4	50	100	0	0	0	0
5Q	SCH_2CH_3	H	H	Q^4	50	100	0	0	0	0
5R	H	H	H	Q^5	80	100	98	98	0	100*
5S	H	H	Cl	Q^5	50	100	90	100*	50	80
5T	H	CF_3	H	Q^5	50	100	0	50	0	80
5U	SCH_2CH_3	H	H	Q^5	50	100	0	60	0	70
Enoxastrobin					50	100	100	98	20	90

* The compound appeared to be phytotoxic.

Table 2
The in vivo fungicidal activity of target compounds **5A–E** and **5J–M** (inhibition %)



No.	Substituents				Testing concentration (mg/L)								
	R^1	R^2	R^3	Q	*E. graminis*			*C. lagenarium*			*P. sorghi* Schw.		
					6.25	1.56	0.39	6.25	1.56	0.39	6.25	1.56	0.39
5A	H	H	H	Q^1	100	30	0	100	85	60	100	80	50
5B	H	H	Cl	Q^1	98	50	0	100	80	40	100	80	70
5C	H	CF_3	H	Q^1	30	0	0	70	0	0	80	60	20
5D	SCH_2CH_3	H	H	Q^1	20	0	0	85	60	10	100	80	50
5E	Cl	H	H	Q^1	50	30	20	100	90	80	70	50	30
5J	H	H	H	Q^3	50	0	0	80	65	30	65	20	0
5K	H	H	Cl	Q^3	95	40	20	95	85	50	95	50	0
5L	H	CF_3	H	Q^3	30	20	0	0	0	0	50	30	0
5M	SCH_2CH_3	H	H	Q^3	40	20	0	60	10	5	20	0	0
Enoxastrobin					100	50	20	90	80	20	98	70	20

against nearly all of the tested fungi at 0.39 mg/L compared to Enoxastrobin. In-depth synthesis and structure optimisation studies are currently underway in our laboratory.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2014.03.024.

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