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Article

Design and Synthesis of Novel 3,4-Dihydro-2*H*-1,2,4-benzothiadiazine 1,1-Dioxides-based Strobilurins as Potent Fungicide Candidates

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Abstract To discover novel strobilurins analogues with good and broad spectrum activity, a series of novel 3,4-dihydro-2*H*-1,2,4-benzothiadiazine 1,1-dioxides-based strobilurins was designed, synthesized, and tested against various phytopathogenic fungi. Compounds **7**b, **7**c, and **7**k exhibited substantial and broad spectrum antifungal activities against the tested phytopathogenic fungi, especially compound **7**b, which showed 100%, 80%, 90%, and 90% antifungal activity(*in virto*) against *Erysiphe graminis*(*E. graminis*), *Puccinia sorghi Schw.*(*P. sorghi Schw.*), *Colletotrichum lagenarium*(*C. lagenarium*), and *Pseudoperonospora cubensis*(*P. cubensis*) at 300 μg/mL, respectively, better or comparable to the positive control azoxystrobin. Moreover, compound **7**b exhibited 85% greenhouse inhibition activity(*in vivo*) against *E. graminis* even at 0.2 μg/mL, equal to azoxystrobin(90%) and trifloxystrobin(90%). Meanwhile, compound **7**b against *P. cubensis* displayed 70% and 55% greenhouse inhibition activity(*in vivo*) at 1.56 and 0.2 μg/mL, respectively, much better than those of azoxystrobin and trifloxystrobin(both 0% at 1.56 and 0.2 μg/mL). Therefore, compound **7**b could be considered as the most promising fungicidal candidate for further study. Furthermore, based on the effective concentration(EC_{50}) against *C. arachidicola*, the built CoMSIA model provided the useful reference for the further structural optimization design.

Keywords Strobilurin; 3,4-Dihydro-2*H*-1,2,4-benzothiadiazine 1,1-dioxide; Fungicidal activity; CoMSIA model

1 Introduction

With growing demand for agricultural products for the rising global population, control of weeds, pathogens, and insect pests remains a constant and critical need[1]. Phytopathogenic fungi and oomycetes have caused dramatic crop yield losses and thus associated with the serious economic losses in crop yields and food security. One extreme example, southern corn leaf blight, caused by *Cochliobolus heterostrophus*, anamorph *Bipolaris maydis*, has led to the annual economic loss over US $1 billion for American corn growers[2]. Another example is that more than 50% cucumber fruit yield losses were attribiuted to cucumber downy mildew, which is caused by *Pseudoperonospora cubensis*[3]. Currently, the application of antifungal agrochemicals remains an effective strategy to fight against phytopathogenic fungi and oomycetes in crop protection for the improvement of yield and quality of agricultural products[4].

Strobilurin fungicides, first isolated from fermentations of *Stroblurus tenacellus* in 1977, have become one of the potent and successful classes of antifungal agrochemicals nowadays[5]. They made up 22.2% of fungicide market with $3.396 billion sales in 2016[6]. Strobilurin fungicides can inhibit mitochondrial respiration through acting on Q_0 of cytochrome *b* of cytochrome *bc*1 complex in fungal respiratory chain, blocking electron transfer, and ultimately leading to cessation of fungal growth[7]. Due to high efficacious, low toxicity, broad spectrum, and suitable for a wide range of crops, so far, more than a dozen strobilurins fungicides have been found, such as azoxystrobin[8], pyraoxystrobin[9], picoxystrobin[10] and enestroburin[11] (Scheme 1), and most of them contain a similar chemical scaffold (*E*)-methyl 3-methoxy-2-phenylacrylate(*β*-methoxyacrylate), which is recognized as a valuable structural core. Despite the formidable advances in strobilurin fungicides, long-term widespread use of conventional strobilurin fungicides has led to resistance of different phytopathogenic fungi and oomycetes[12]. Therefore, to resolve the worsening control problems of phytopathogenic fungi and oomycetes with strobilurin fungicides, the development of novel strobilurin fungicides is very important to agrochemistry.

Heterocyclic ring as a substructure is a very important method for novel pesticide discovery[13]. 3,4-Dihydro-2*H*-

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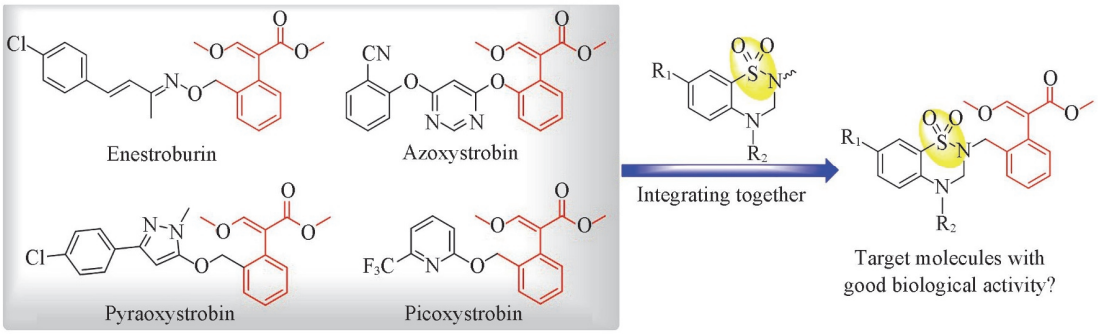
1,2,4-benzothiadiazine 1,1-dioxides are a remarkably important class of fused heterocyclic scaffolds, possessing environmental compatibility and a wide range of desirable biological and pharmacological activities, such as antibacterial[14], antioxidant[15], anticancer[16], aldose reductase inhibitors[17], and positive allosteric modulators[18]. Furthermore, 3,4-dihydro-2*H*-1,2,4-benzothiadiazine 1,1-dioxides contain the sulfonamide moiety, and belong to the class of cyclic sulfonamides. As a highly efficient pharmacophore, sulfonamide has been widely used in medicine and pesticide drug design and has broad-spectrum biological activities, such as antifungal[19,20], insecticidal[21], antiviral activity activities[22—24], and anti-HIV[25]. Meanwhile, sulfonamide has a hydrogen bond acceptor site and a hydrophilic core and thus it could be able to form hydrogen bond with enzymes in organism to display various unknown and interesting biological activities. Therefore, 3,4-dihydro-2*H*-1,2,4-benzothiadiazine 1,1-dioxides maybe are potential plant defense response lead scaffolds.

Inspired by the above, with the goal of developing novel strobilurin derivatives by combining the active scaffold of strobilurin fungicides[(*E*)-methyl 3-methoxy-2-phenylacrylate] and 1,2,4-benzothiadiazine 1,1-dioxides as active substructures, a series of novel 3,4-dihydro-2*H*-1,2,4-benzothiadiazine 1,1-dioxides-based strobilurins was rationally designed and synthesized(Scheme 1). The preliminary antifungal activities results indicated that title compounds exhibited good to excellent activities against one or multiple phytopathogenic fungi. Moreover, the CoMSIA model was built based on the effective concentration(EC_{50}) against *C.arachidicola*.



Scheme 1 Design of the title compounds

2 Experimental

2.1 Materials and Instruments

The melting points were determined on an X-4 binocular microscope melting point apparatus(Beijing Tech Instrument Co., Beijing, China) and were uncorrected. ^1H and ^{13}C nuclear magnetic resonance(NMR) spectra were recorded at 400 MHz using a Bruker AV 400 spectrometer(Bruker Co., Switzerland) in $CDCl_3$ or DMSO-d_6 solution with tetramethylsilane(TMS) as the internal standard. High-resolution mass spectrometry (HRMS) data were obtained on a Varian QFT-ESI instrument. Flash chromatography was performed with silica gel(200—300 mesh). The reagents were all analytically pure. All solvents and liquid reagents were dried by standard methods in advance and distilled before use.

2.2 Synthesis Procedure

2.2.1 General Synthesis Procedure for Compounds 2a—2h

Compound **1**(5 mmol) and stannous chloride dihydrate (3.385 g, 15 mmol) were added to a three-necked flask containing anhydrous ethanol(30 mL), and the reaction was refluxed for 1—2 h and concentrated *in vacuo*. Ethyl acetate (20 mL) was added to the residue, and the mixture was poured into ice water(30 mL). Then sodium bicarbonate was added to adjust the pH to 8. The mixture was filtered through the diatomite, and washed with ethyl acetate. The filtration was concentrated to afford compounds **2**a—**2**h.

2.2.2 General Synthesis Procedure for Compounds 3a—3i

The intermediate **2**(4 mmol) was heated in triethyl orthoformate(15 mL) to reflux for 3—4 h. After the reaction was completed and cooled to room temperature, a large amount of solid appeared. Then the solid was collected by filtration, washed with diethyl ether(20 mL), and dried to obtain compounds **3**a—**3**h. The 7-nitro substituted compound **3**i was synthesized by nitration of intermediate **3**a according to the reference[26].

2.2.3 General Synthesis Procedure for Compounds 4a—4r

Potassium carbonate(6 mmol) was added to a solution of intermediate **3**(3 mmol) in acetonitrile(25 mL), followed by the dropwise addition of alkyl iodide(3 mmol) in acetonitrile (5 mL). Then the reaction was heated to 55 °C and monitored by thin layer chromography(TLC). After the reaction was completed, the solvent was removed *in vacuo*. The residue was suspended in water(20 mL), and the resulting insoluble material was filtrated. The crude solid obtained was washed with water (20 mL), and dried to afford compounds **4**a—**4**r.

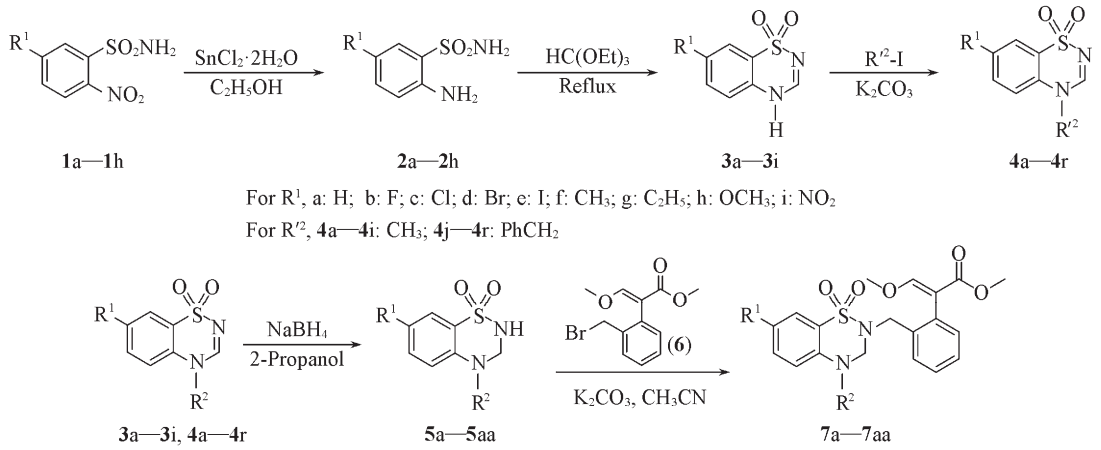
2.2.4 General Synthesis Procedure for Compounds 5a—5aa

Sodium borohydride(0.303 g, 8 mmol) was slowly added to a solution of the intermediate **3** or **4**(2 mmol) in 2-propanol(20 mL) under stirring at room temperature. After 0.5 h, the solvent was removed *in vacuo* and the residue was

suspended in water(20 mL). The mixture was adjusted to pH 3 with 2 mol/L HCl, and a large amount of solid appeared. Then the solid was collected by filtration, washed with water(20 mL), and dried to obtain compounds **5**a—**5**aa.

2.2.5 General Synthesis Procedure for Compounds 7a—7aa

Potassium carbonate(2 mmol) was added to a solution of intermediate **5**(1 mmol) in acetonitrile(15 mL), followed by the dropwise addition of compound **6**(1 mmol) in acetonitrile (5 mL). Then the reaction was heated to 70 °C and monitored by TLC. After the reaction was completed, the solvent was removed *in vacuo.* The residue was purified on silica gel with petroleum ether/ethyl acetate(3:1, volume ratio) to obtain title compounds **7**a—**7**aa. The synthetic routes of compounds **7**a—**7**aa are shown in Scheme 2.



7a: R^1=H, R^2=H; **7**b: R^1=F, R^2=H; **7**c: R^1=Cl, R^2=H; **7**d: R^1=Br, R^2=H; **7**e: R^1=I, R^2=H; **7**f: R^1=CH_3, R^2=H; **7**g: R^1=C_2H_5, R^2=H; **7**h: R^1=OCH_3, R^2=H; **7**i: R^1=NO_2, R^2=H; **7**j: R^1=H, R^2=CH_3; **7**k: R^1=F, R^2=CH_3; **7**l: R^1=Cl, R^2=CH_3; **7**m: R^1=Br, R^2=CH_3; **7**n: R^1=I, R^2=CH_3; **7**o: R^1=CH_3, R^2=CH_3; **7**p: R^1=C_2H_5, R^2=CH_3; **7**q: R^1=OCH_3, R^2=CH_3; **7**r: R^1=NO_2, R^2=CH_3; **7**s: R^1=H, R^2=$PhCH_2$; **7**t: R^1=F, R^2=$PhCH_2$; **7**u: R^1=Cl, R^2=$PhCH_2$; **7**v: R^1=Br, R^2=$PhCH_2$; **7**w: R^1=I, R^2=$PhCH_2$; **7**x: R^1=CH_3, R^2=$PhCH_2$; **7**y: R^1=C_2H_5, R^2=$PhCH_2$; **7**z: R^1=OCH_3, R^2=$PhCH_2$; **7**aa: R^1=NO_2, R^2=$PhCH_2$

Scheme 2 Synthetic routes of compounds 7a—7aa

2.3 Fungicidal Activity Screening

The fungicidal activities(*in vitro*) of the title compounds **7**a—**7**aa against *Cercospora arachidicola*(*C. a*), *Alternaria solani*(*A. s*), *Physalospora piricola*(*P. p*), *Gibberella zeae*(*G. z*), *Phytophthora infestans(*Mont) de Bary(*P. i*), *Botrytis cinerea* (*B. c*), *Rhizoctonia cerealis*(*R. c*), *Pellicularia sasakii*(*P. s*), and *Sclerotinia sclerotiorum*(*S. s*) were determined *in vitro* at 50 μg/mL by the mycelium growth rate test according to the reference[27]. The growth inhibition rates were calculated using the following formula: $I(\%)=(C-T)/C\times100\%$, in which I is the growth inhibition rate(%), C and T are the control settlement radius(mm) and treatment group fungus settlement radius(mm), respectively. Water was used as the blank control, and azoxystrobin as a positive control. The median EC_{50}'s of the title compounds **7**a—**7**aa against *Cercospora arachidicola* were determined according to ref.[28].

The fungicidal activities(*in vivo*) of title compounds **7**a—**7**aa against *Erysiphe graminis*, *Puccinia sorghi Schw*., *Colletotrichum lagenarium*, and *Pseudoperonospora cubensis* were determined by fungal spore inoculation according to the reported method[29]. The percentage of disease control was compared with the control plants, where 100 means complete disease control and 0 means no disease control. Water was used as the blank control, and azoxystrobin as a positive control.

2.4 CoMSIA Calculation Methods

The CoMSIA studies were carried out using a SYBYL-X 2.0 software from Tripos Inc.(St. Louis, MO, USA). All molecules were built with the SKETCH option in SYBYL under default settings. CoMSIA contour maps were generated with partial least-squares coefficients[30]. The partial least-square was carried out to establish a linear relationship. Cross-validation was performed by using the "leave-one-out" method to obtain the cross-validated coefficient q^2 and optimal number of component. The non-cross-validated correlation coefficient r^2 and cross-validated coefficient q^2 could estimate the predictive capability and modelling, respectively.

3 Results and Discussion

3.1 Chemistry

2-Aminobenzenesulfonamides(**2**a—**2**h) were synthesized in yields of 73%—83% through a reduction reaction between tin(II) dichloride and 2-nitrobenzenesulfonamides(**1**a—**1**h). Intermediates(**2**a—**2**h) were converted to the corresponding 4*H*-benzo[*e*][1,2,4]thiadiazine 1,1-dioxides(**3**a—**3**h) by refluxing with triethyl orthoformate. However, 7-nitro-4H-benzo[*e*]-[1,2,4]thiadiazine 1,1-dioxide(**3**i) cannot be prepared through the above method due to the strong electron-withdrawing property of NO_2 group. Finally, compound **3**i was synthesized by nitration of intermediate **3**a according to ref.[26]. Compounds **3**a—**3**i were converted to the corresponding 4-methyl/benzyl-4*H*-benzo[*e*][1,2,4]thiadiazine 1,1-dioxides (**4**a—**4**r) through reacting with alkyl iodide in the presence of potassium carbonate in anhydrous acetonitrile. The C═N double bond of compounds **3**a—**3**i or **4**a—**4**r was reduced by

sodium borohydride to obtain compounds **5**a—**5**aa with high yields ranging from 81% to 89%. The title compounds **7**a—**7**aa were prepared by a nucleophilic substitution reaction between compounds **5**a—**5**aa and methyl (*E*)-2-[2-(bromomethyl)-phenyl]-3-methoxyacrylate(**6**) with potassium carbonate as base in yields of 41%—80%. Their chemical structures were confirmed by ^{1}H NMR, ^{13}C NMR, and HRMS(see the Electronic Supplementary Material of this paper).

3.2 Antifungal Activities

The antifungal activities(*in vitro*) of the title compounds **7**a—**7**aa are listed in Table 1. The results of preliminary bioassays indicated that most title compounds showed moderate to good antifungal activities at the concentration of 50 mg/L, and even better than the positive control azoxystrobin, especially compounds **7**b, **7**c, and **7**k, which exhibited substantial and broad spectrum antifungal activities against the tested phytopathogenic fungi. Findings indicated antifungal activity varied remarkably depending upon substituents R^1 and R^2. Looking from the overall, the order of R^2 related to the antifungal activity of title compounds was H>CH_3>$PhCH_2$, when title compounds with the same R^1, indicating that more bulk effect relative to a hydrogen substituent in the R^2 group is unfavourable to the antifungal activity. In general, when the substituent R^2 was the same, title compounds **7**b, **7**k, and **7**t with R^1(R^1=F) showed more better antifungal activity than others, revealing that a fluorine substituent in the R^1 could improve the antifungal activity.

Table 1 *In vitro* fungicidal activities of title compounds 7a—7aa*

Compd.	Substituent		*In vitro* fungicidal activity(%) at 50 μg/mL								
	R^1	R^2	*C. a*	*A. s*	*P. p*	*G. z*	*P. i*	*B. c*	*R. c*	*P. s*	*S. s*
7a	H	H	66.6	44.2	48.3	41.2	53.6	48.6	65.3	43.6	50.9
7b	F	H	78.7	64.7	72.5	89.7	90.4	60.3	77.8	67.9	83.2
7c	Cl	H	67.0	53.3	50.2	55.2	55.1	53.6	58.5	51.3	60.7
7d	Br	H	59.3	33.5	47.2	45.3	50.2	45.3	40.5	43.8	52.6
7e	I	H	48.9	29.1	41.7	38.2	30.7	38.5	20.6	30.6	30.2
7f	CH_3	H	42.5	30.3	43.2	35.1	48.7	39.4	37.3	46.9	48.9
7g	C_2H_5	H	35.7	24.8	36.8	23.6	45.3	29.3	33.5	40.2	42.3
7h	OCH_3	H	30.7	20.4	29.5	30.2	25.1	9.7	20.1	32.0	32.5
7i	NO_2	H	55.3	40.5	45.3	23.7	13.6	17.5	39.7	18.7	45.6
7j	H	CH_3	55.3	34.2	63.7	48.9	68.3	53.2	49.7	47.5	54.7
7k	F	CH_3	72.2	50.4	65.3	67.4	67.4	58.3	50.0	50.3	73.2
7l	Cl	CH_3	62.3	37.7	54.1	60.3	56.7	44.2	40.3	40.8	49.5
7m	Br	CH_3	54.1	31.2	47.2	47.3	43.8	32.1	35.6	35.2	32.6
7n	I	CH_3	43.1	25.8	45.2	30.1	26.5	19.4	19.3	32.1	30.2
7o	CH_3	CH_3	38.4	26.7	29.4	35.7	23.9	23.3	34.5	40.1	35.7
7p	C_2H_5	CH_3	29.1	23.2	19.8	26.8	18.2	19.7	20.1	23.2	36.5
7q	OCH_3	CH_3	21.6	12.7	7.6	37.5	18.7	10.0	15.4	10.3	25.0
7r	NO_2	CH_3	49.7	35.7	12.4	31.9	7.9	19.8	27.3	17.5	29.4
7s	H	$PhCH_2$	35.2	24.1	32.1	35.6	26.9	31.5	37.2	32.6	40.3
7t	F	$PhCH_2$	45.2	27.5	31.6	41.2	36.7	32.3	38.5	27.8	39.5
7u	Cl	$PhCH_2$	33.7	23.6	20.7	33.1	20.5	24.2	30.2	20.5	28.9
7v	Br	$PhCH_2$	24.1	21.0	21.0	27.5	20.7	20.1	28.5	19.4	27.5
7w	I	$PhCH_2$	19.2	19.3	9.3	10.6	10.5	17.4	10.4	10.3	13.6
7x	CH_3	$PhCH_2$	19.1	20.6	12.9	24.7	15.4	10.3	20.3	23.6	29.0
7y	C_2H_5	$PhCH_2$	13.2	16.7	8.7	23.7	14.0	13.7	19.4	20.9	28.4
7z	OCH_3	$PhCH_2$	10.5	8.9	12.9	20.4	10.5	5.0	9.7	19.3	9.6
7aa	NO_2	$PhCH_2$	28.6	20.6	18.3	19.7	7.6	15.8	17.6	15.6	12.7
Azoxystrobin			52.3	44.2	63.8	90.6	92.5	80.2	91.8	82.4	92.5

* *C. a: Cercospora arachidicola; A. s: Alternaria solani; P. p: Physalospora piricola; G. z: Gibberella zeae; P. i: Phytophthora infestans(Mont) de Bary; B. c: Botrytis cinerea; R. c: Rhizoctonia cerealis; P. s: Pellicularia sasakii; S. s: Sclerotinia sclerotiorum.*

The antifungal activities(*in vivo*) of the title compounds **7**a—**7**aa against *E. graminis*, *P. sorghi Schw.*, *C. lagenarium*, and *P. cubensis* at 300 μg/mL are displayed in Table 2. Compounds **7**b and **7**k exhibited excellent and broad spectrum antifungal activities against the tested four phytopathogenic fungi, especially compound **7**b, which showed 100%, 80%, 90%, and 90% antifungal activities against *E. graminis*, *P. sorghi Schw.*, *C. lagenarium*, and *P. cubensis*, respectively, comparable to the positive control azoxystrobin. The results indicated that the introduction of a fluorine group in R^1 and a hydrogen group in R^2 can effectively improve the antifungal activity(*in vivo*). All title compounds **7**a—**7**aa displayed better fungicidal activity against *P. sorghi Schw.* than that of azoxystrobin. In addition, the structure activity relationship(*in vivo* antifungal activity) is similar to that of the antifungal activity(*in vitro*).

Subsequently, title compounds **7**b and **7**k with excellent antifungal activities(*in vivo*) were selected for further bioassay in the greenhouse at the concentrations of 100, 12.5, 1.56, and 0.2 μg/mL, and the results are shown in Fig.1. Compound **7**k

displayed lower antifungal activity against *E. graminis*, *P. sorghi Schw.*, and *C. lagenarium* than that of azoxystrobin, whereas compound **7**k exhibited 50% antifungal activity against *P. cubensis* at 100 μg/mL, better than those of the positive controls(azoxystrobin with 10% inhibition and trifloxystrobin with 30% inhibition). Compound **7**b displayed excellent inhibition activity against *E. graminis and P. cubensis*. Compound **7**b against *E. graminis* showed 85% antifungal activity even at 0.2 μg/mL, similar to azoxystrobin(90%) and trifloxystrobin(90%). In addition, compound **7**b against *P. cubensis* displayed 70% and 55% greenhouse inhibition activity(*in vivo*) at 1.56 and 0.2 μg/mL, respectively, whereas azoxystrobin and trifloxystrobin with 0% inhibition ratio at 1.56 and 0.2 μg/mL. Thus, compound **7**b could be considered as the most promising fungicidal candidate for further development.

Table 2 *In vivo* fungicidal activities of title compounds 7a—7aa*

Compd.	*In vivo* fungicidal activity(%) at 300 μg/mL			
	E. g	*P. s*	*C. l*	*P. c*
7a	60	55	50	40
7b	100	80	90	90
7c	70	60	55	50
7d	45	40	35	35
7e	20	25	20	10
7f	40	35	0	20
7g	30	30	0	10
7h	0	30	20	0
7i	45	30	40	50
7j	60	50	50	30
7k	90	80	75	75
7l	60	50	50	40
7m	60	40	20	40
7n	20	10	0	0
7o	20	20	10	0
7p	10	15	0	0
7q	0	30	10	0
7r	30	35	30	25
7s	20	30	30	20
7t	40	40	45	30
7u	30	30	20	15
7v	10	20	20	20
7w	0	10	0	0
7x	10	10	10	0
7y	0	10	0	0
7z	0	10	0	0
7aa	20	15	20	10
Azoxystrobin	100	5	80	75

* *E. g: Erysiphe graminis; P. s: Puccinia sorghi Schw.; C. l: Colletotrichum lagenarium; P. c: Pseudoperonospora cubensis.*

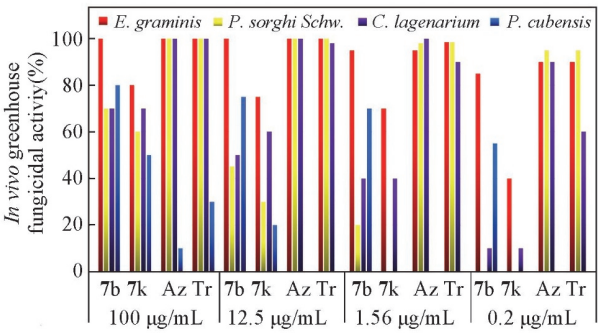


Fig.1 Greenhouse fungicidal activity(*in vivo*) of title compounds 7b and 7k, azoxystrobin(Az), and trifloxystrobin(Tr)

3.3 3D-QSAR

The median EC_{50}'s of title compounds **7**a—**7**aa against *C. arachidicola* were tested and the results are listed in Table S1(see the Electronic Supplementary Material of this paper). Based on the negative logarithm of EC_{50}(pEC_{50}), a brief CoMSIA model was established. Compound **7**b had the lowest EC_{50} value and was used as the template molecule. Compounds **7**c, **7**i, **7**j, **7**m, **7**r, and **7**u were picked randomly as the test set. A correlation coefficient of r^2=0.988 and a cross validated coefficient of q^2=0.807 were obtained as the best CoMSIA model. The optimal number of components, the standard error of estimate and the *F* values were 8, 0.067 and 156.985, respectively. Electrostatic, steric, hydrophobic, H-bond donor, and H-bond acceptor fields were calculated to build the CoMSIA model, and the order of the relative contribution to the full model was steric(46.3%)>H-bond donor(25.2%)>hydrophobic(19.9%)>electrostatic(6.4%)>H-bond acceptor(2.2%), revealing that the antifungal activity was mostly affected by steric, H-bond donor and hydrophobic fields.

CoMSIA contour maps are exhibited in Fig.2 to visualize how steric, H-bond donor and hydrophobic fields contribute to the antifungal activity. The yellow regions in the steric CoMSIA contour map[Fig.2(A)] indicated that the bulk groups in the areas were unfavourable to the antifungal activity, which is consistent with the bioactivity data, such as the group R^1 with the same substituent, the antifungal activity in the sequence of R^2: H>CH_3>$PhCH_2$. As for the H-bond donor CoMSIA contour map in Fig.2(B), the hydrogen bond acceptor groups in the blue-green areas were favourable. Analysis of the H-bond donor CoMSIA contour plots suggested that the a hydrogen substituent in the R^2 group was important for the

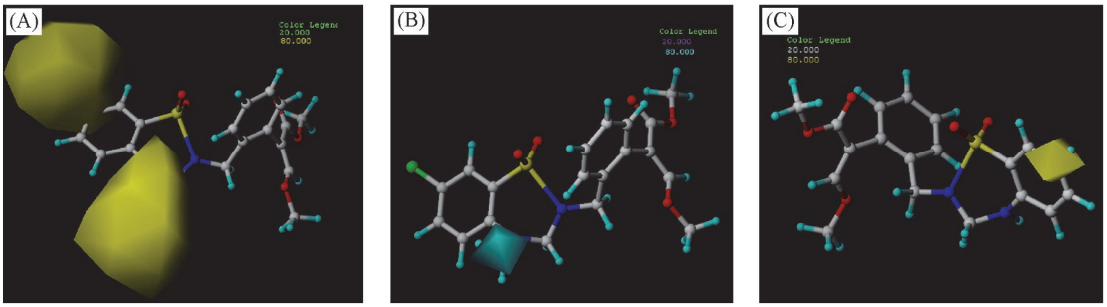


Fig.2 Contour plots of the CoMSIA steric field(A), H-bond donor field(B) and hydrophobic field(C)

antifungal activity, such as the title compounds(R^2=H) with the same R^1, showing better antifungal activity against *C. arachidicola* than other compounds(R^2=CH_3 or $PhCH_2$). The hydrophobic CoMSIA contour map is shown in Fig.2(C), and the yellow regions represented that the hydrophobic groups were beneficial to the antifungal activity. These results of CoMSIA contour maps indicated that the substituent R^1 was a hydrophobic group, and the substituent R^2 was a hydrogen bond donor group with small volume, which could improve the antifungal activity against *C. arachidicola*, providing the useful reference for the further structural optimization design.

4 Conclusions

In conclusion, 27 novel 3,4-dihydro-2*H*-1,2,4-benzothiadiazine 1,1-dioxides-based strobilurins were designed, synthesized, and characterized by ^{1}H NMR, ^{13}C NMR, and HRMS. Most title compounds displayed moderate to excellent antifungal activities, especially compounds **7**b, **7**c and **7**k. Moreover, the antifungal activities of compound **7**b was better or comparable to the positive control azoxystrobin or trifloxystrobin. Hence compound **7**b could be regarded as the most promising antifungal molecule for further study. The 3D-QSAR study results indicated that except for R^1 group being a hydrophobic group, R^2 was a hydrogen bond donor group, and the introduction of fluorine group can also improve the antifungal activity of target compounds(for example, compounds **7**b and **7**k). Therefore, for the next lead structure optimization, we will introduce the trifluoromethyl, multi-fluoroalkyl groups or fluorine in different position of the benzene ring for the lead structure.

Electronic Supplementary Material

Supplementary material is available in the online version of this article at http://dx.doi.org/10.1007/s40242-020-0160-9.

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