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Novel Benzo-1,2,3-thiadiazole-7-carboxylate Derivatives As Plant Activators and the Development of Their Agricultural Applications

Qingshan Du, Weiping Zhu, Zhenjiang Zhao,* Xuhong Qian, and Yufang Xu*

Shanghai Key Laboratory of Chemical Biology, School of Pharmacy, East China University of Science and Technology, P.O. Box 544, 130 Meilong Road, Shanghai 200237, China

ABSTRACT: Plant activators are a novel kind of agrochemicals that could induce resistance in many plants against a broad spectrum of diseases. To date, only few plant activators have been commercialized. In order to develop novel plant activators, a series of benzo-1,2,3-thiadiazole-7-carboxylate derivatives were synthesized, and the structures were characterized by ^{1}H NMR, IR, elemental analyses, and HRMS or MS. Their potential systemic acquired resistance as plant activators was evaluated as well. Most of them showed good activity, especially, fluoro-containing compounds **3d** and **3e**, which displayed excellent SAR-inducing activity against cucumber *Erysiphe cichoracearum* and *Colletotrichum lagenarium* in assay screening. Field test results illustrated that compounds **3d** and **3e** were more potent than the commercial plant activator, *S*-methyl benzo[1,2,3]thiadiazole-7-carbothioate (BTH) toward these pathogens. Further, the preparation of compound **3d** is more facile than BTH with lower cost, which will be helpful for further applications in agricultural plant protection.

KEYWORDS: *benzo-1,2,3-thiadiazole-7-carboxylate derivatives, system acquired resistance, plant activator, field test*

INTRODUCTION

Crop plants must defend against a variety of aggressive pathogens during their life period, including fungi, viruses, bacteria, etc. The diseases caused by these organisms can lead to lethal consequences to plants or great losses in agriculture.[1,2] Traditional agrochemicals play a critical role in the control of these diseases; however, they could cause negative effects on the environment and induce drug resistance. Comparatively, plant activators have attracted much interest for their capabilities of inducing system acquired resistance (SAR) in plants. Other than killing the pathogens directly, plant activators could induce the immunity in plants and thus provide defense against a broad spectrum of diseases.[3−5] To date, a variety of plant activators have been reported,[6−9] of which the most successful one is the commercial plant activator *S*-methyl benzo[1,2,3]thiadiazole-7-carbothioate (BTH). By activating the SAR downstream of salicylic acid (SA), BTH could sensitize various plants against pathogen infection.[10] Structure−activity relationship investigation found that the benzothiadiazole skeleton with a 7-carboxylate group is essential to the high activity, and the induced resistance activity is generally decided by the ester group with a tendency that the higher the molecular weight of the carboxylate derivative, the lower the activity.[11] However, there were only limited compounds synthesized based on the modification of the 7-ester group;[12,13] thus, it is of great significance to evaluate the influence of ester groups on the induced resistance activity and further develop novel and potent plant activators.

Up to now, only limited compounds with high SAR activity have been reported, and the agricultural applications of plant activators are far from developed.[14−16] In our previous work, a series of benzo-1,2,3-thiadiazole carboxylic ester derivatives were synthesized based on the modification of its carboxylate moiety as potent taxoid biosynthesis elicitors in *T. chinensis* cell cultures,[17] and the results showed that the introduction of fluorine-containing groups on the ester moiety significantly increased the taxoid eliciting activity, which corresponded well to the level of their induced cell defense responses. Similar mode of action of elicitors in in-vitro plant cell culture and plant activators in in-vivo plant protection made us exploit these active compounds as potential plant activators.[18] In this study, we aim to discover new potential plant activators with high SAR inducing activity and develop novel plant activators for agricultural applications. Therefore, a series of benzo-1,2,3-thiadiazole-7-carboxylate derivatives were synthesized. Their potential systemic acquired resistance as plant activators was evaluated by 2 phases of screening assays. Also, fluoro-containing compounds, **3d** and **3e**, were evaluated in field tests against *Pseudoperonospora cubensis* and *Erysiphe cichoracearum* on cucumber (*Cucumis sativus* L.) in 4 different locations during 2 years.

MATERIALS AND METHODS

Melting points were recorded on a Büchi B540 apparatus (Büchi Labortechnik AG, Flawil, Switzerland) and are uncorrected. The ^{1}H NMR spectra were recorded on a Bruker AM-500 (500 MHz) spectrometer with DMSO-d_6 as the solvent and TMS as internal standard. Chemical shifts are reported in δ (parts per million) values. The MS spectra were measured with a HRMS Micromass GCT CA 055 spectrometer. The elemental analysis data were measured by an Elementar vario EL III analyzer. Triethylamine was dried over KOH and distilled. BTH (Actigard 50WG) was purchased from Syngenta (China) Co. Ltd. Fifty percent Dimethomorph (WP) was purchased from BASF CO., Ltd., and 12.5% Myclobutanil (EC) was purchased from Pilot Plant of Shenyang Research Institute of Chemical Industry.

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All other solvents and chemicals were of reagent grade and used without further purification.

Field tests were carried out in four locations including Beijing (two sites), Liaoning province, and Shandong province during two years.

Synthesis of Compounds 3b−3e and 5a−5m. The starting compound **1** was synthesized according to the literature description.[19] The synthesis of compound **3c** and the general synthetic procedures of other test compounds were described in our previous work, along with the detailed physical properties and structural data of compounds **3b−3e** and **5a−5d**.[17] Data of earlier unreported compounds were described, as shown in Tables 1 and 2.

Biological Assay Screening. The antimicrobial activity and the SAR activity of the target compounds were evaluated according to the following procedures.

Antimicrobial Activity Screening. A stock solution of each compound was prepared by dissolving the compound in *N*,*N*-dimethylformamide (DMF) to form a concentration of 1000 mg/L. Then a working solution of 100 mg/L was prepared by mixing 1 mL of the stock solution with 9 mL of potato dextrose agar (PDA) culture media thoroughly in a Petri dish. The PDA medium was thoroughly mixed by turning around the Petri dish in a sterilized operation desk 5 times to scatter the compounds in PDA evenly. After that, the fungi cake was inoculated on the plate and incubated in the culture tank at 24−26 °C. Distilled water was used as the control or check (CK). The diameter of fungal spread was measured after 2 days. Growth inhibition was then calculated using the corresponding control. Microorganisms used in this study included *Pyricularia oryzae*, *Bipolaris maydis*, *Colletotrichum lagenarium*, and *Xanthomonas oryzae*.

System Acquired Resistance Screening. After direct antimicrobial activity screening, the SAR activity was determined as well. In order to screen out the new compounds effectively, the screening was conducted in three steps. In the first screening, all compounds were tested with comparatively high concentrations to avoid skipping any potential active compounds. After that, compounds with potential SAR activity were tested with lower concentration in the second assay screening to screen out compounds with high activity. Furthermore, the compounds with high activity and facile preparation were chosen for field tests to exploit their agricultural applications.

Table 1. Yield, Melting Point, IR, and Elemental Analysis Data of the Target Compounds

				elemental analysis					
				requires			found		
compd	yield (%)	mp (°C)	IR (cm^{-1})	C	H	N	C	H	N
5e	55	88−89	ν 1715, 1300, 1100, 780	55.49	3.20	8.09	55.35	3.35	8.17
5f	56	84−85	ν 1720, 1300, 1105, 785	44.22	2.73	6.88	47.49	2.80	6.94
5g	60	112−113	ν 1715, 1300, 1100	42.53	2.44	6.17	42.53	2.53	6.18
5h	57	76−78	ν 3089, 2950, 1720, 1599, 1503, 1406, 1265, 1130, 1095, 1045, 870, 700	55.49	3.20	8.09	55.74	3.18	8.18
5i	57	100−102	ν 3089, 2955, 1707, 1592, 1558, 1488, 1406, 1272, 1205, 1130, 1080, 860, 805, 760, 680	52.97	3.06	7.72	53.20	3.10	7.71
5j	52	101−103	ν 3119, 2956, 1733, 1603, 1521, 1430, 1340, 1268, 1120, 1060, 860, 770, 720	51.47	2.97	11.26	51.69	3.10	11.17
5k	52	125−127	ν 3089, 2963, 1710, 1636, 1562, 1495, 1400, 1295, 1370, 1030, 980, 840, 756, 680	61.01	3.98	7.90	61.22	3.90	8.02
5l	50	92−93	ν 1710, 1310, 1100, 770	57.03	3.94	7.82	57.03	4.03	8.20
5m	56	119−120	ν 3059, 2955, 1766, 1703, 1558, 1484, 1410, 1298, 1180, 1087, 900, 810, 770, 720	47.79	2.83	6.55	47.90	2.58	6.36

Table 2. ^{1}H NMR and HRMS/MS Data of the Target Compounds

compd	^{1}H NMR (solvent: DMSO-d_6)	HRMS/MS (EI)
5e	δ 4.69−4.76 (m, 4H, OCH_2CH_2O), 7.22 (t, 1H, *J* = 7.5, Ar−H), 7.22 (t, 1H, *J* = 8.6 Hz, Ar−H), 7.50−7.53 (m, 1H, Ar−H), 7.78 (t, 1H, *J* = 7.8 Hz, Ar−H), 7.94 (td, 1H, J_1 = 7.5, J_2 = 1.5, Ar−H), 8.47 (d, 1H, *J* = 7.3 Hz, Ar−H), 8.88 (d, 1H, *J* = 7.3, Ar−H)	[M^+], 346.04; found, 346.00
5f	δ 4.67−4.76 (m, 4H, OCH_2CH_2O), 7.52−7.56 (m, 2H, Ar−H), 7.77−7.80 (m, 1H, Ar−H), 7.78−7.86 (m, 1H, Ar−H), 8.02 (t, 1H, *J* = 7.8 Hz, Ar−H), 8.54 (d, 1H, *J* = 7.3 Hz, Ar−H), 9.12 (d, 1H, *J* = 8.4 Hz, Ar−H)	[M^+], 407.96; found (M-N_2), 380.00
5g	δ 4.69−4.76 (m, 4H, OCH_2CH_2O), 7.1−7.2 (m, 1H, Ar−H), 7.48 (t, 1H, *J* = 7.4 Hz, Ar−H), 7.75 (dd, 1H, J_1 = 7.7 Hz, J_2 = 1.4 Hz, Ar−H), 7.96 (t, 1H, *J* = 7.7 Hz, Ar−H), 7.99 (t, 1H, *J* = 7.7 Hz, Ar−H), 8.48 (d, 1H, *J* = 7.3 Hz, Ar−H), 9.04 (d, 1H, *J* = 8.2 Hz, Ar−H)	HRMS [M^+], 453.9490; found, 453.9484
5h	δ 4.67−4.79 (m, 4H, OCH_2CH_2O), 7.31−7.35 (m, 2H, Ar−H), 7.94 (dd, 1H, J_1 = 7.8 Hz, J_2 = 7.3 Hz, Ar−H), 8.01−8.05 (m, 2H, Ar−H), 8.44 (d, 1H, *J* = 7.3 Hz, Ar−H), 9.04 (d, 1H, *J* = 7.8 Hz, Ar−H)	HRMS [M^+], 346.0424; found, 346.0389
5i	δ 4.68−4.79 (m, 4H, OCH_2CH_2O), 7.57 (d, 2H, *J* = 8.5 Hz, Ar−H), 7.94 (dd, 1H, J_1 = 8.3 Hz, J_2 = 7.3 Hz, Ar−H), 7.96 (d, 2H, *J* = 8.5 Hz, Ar−H), 8.44 (d, 1H, *J* = 7.3 Hz, Ar−H), 9.04 (d, 1H, *J* = 8.3 Hz, Ar−H)	HRMS [M^+], 362.0128; found, 362.0128
5j	δ 4.74−4.80 (m, 4H, OCH_2CH_2O), 7.94 (dd, 1H, J_1 = 7.3 Hz, J_2 = 8.4 Hz, Ar−H), 8.19 (d, 2H, *J* = 8.6 Hz, Ar−H), 8.32 (d, 2H, *J* = 8.6 Hz, Ar−H), 8.43−8.45 (d, 1H, *J* = 7.3 Hz, Ar−H), 9.02−9.04 (d, 1H, *J* = 8.4 Hz, Ar−H)	[M^+], 373.04; found, 373.10
5k	δ 4.56−4.70 (m, 4H, OCH_2CH_2O), 6.68 (d, 1H, *J* = 16.0 Hz, =CH−), 7.36−7.42(m, 3H, Ar−H), 7.65−7.69 (m, 3H, =CH- and Ar−H), 7.94 (dd, 1H, J_1 = 7.3 Hz, J_2 = 8.2 Hz, Ar−H), 8.44 (d, 1H, *J* = 7.3 Hz, Ar−H), 9.03 (d, 1H, *J* = 8.2 Hz, Ar−H)	HRMS [M^+], 354.0674; found, 354.0659
5l	δ 4.69−4.78 (m, 4H, OCH_2CH_2O), 6.98−7.00 (m, 2H, Ar−H), 7.78 (t, 1H, *J* = 7.8 Hz, Ar−H), 7.83 (dd, 1H, J_1 = 7.9 Hz, J_2 = 1.8 Hz, Ar−H), 8.44 (d, 1H, *J* = 7.3 Hz, Ar−H), 8.86 (d, 1H, *J* = 8.2 Hz, Ar−H)	HRMS [M^+], 358.0599; found, 358.0623
5m	δ 4.55−4.64 (m, 4H, OCH_2CH_2O), 4.99 (s, 2H, CH_2), 7.06 (d, 1H, *J* = 9.0 Hz, Ar−H), 7.13 (d, 1H, *J* = 8.9 Hz, Ar−H), 7.42 (s, 1H, Ar−H), 7.93 (dd, 1H, J_1 = 8.3 Hz, J_2 = 7.3 Hz, Ar−H), 8.35 (d, 1H, *J* = 7.3 Hz, Ar−H), 9.05 (d, 1H, *J* = 8.3 Hz, Ar−H)	[M^+], 425.98; found, 426.00

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First Assay Screening. The microorganisms used in the first screening include *Pyricularia oryzae*, *Bipolaris maydis*, *Colletotrichum lagenarium*, *Erysiphe cichoracearum*, and a bacterium, *Xanthomonas oryzae*. All compounds were tested with a concentration of 500 mg/L except for **3c**, the self-synthesized plant activator BTH. As a potent plant activator, 200 mg/L **3c** was used in the first screening as the positive control. The systemic acquired resistance activity of each test compound was measured using the backward method: plants were treated with test compounds for four times separately at 7, 5, 3, and 1 day before inoculation. After inoculation, the plants were cultured for 7 days, and the visual-lesions on the inoculated leaves were recorded.[20] Three repeated tests were performed for each compound. In every repeated test, five plants were used for the test of each compound. Double-distilled water and **3c** (BTH) were used as CK and positive control. Determination of SAR activity of the tested compounds against testing microorganisms was conducted according to the following procedures.

Xanthomonas oryzae. Two month-old rice seedlings were chosen for the screening. After treatment with test compounds for 4 times as described above, the bacterium was inoculated using an acupuncture inoculation method on the day after the last treatment. Then the plants were cultured at 25 °C for 7 days with 100% humidity. The lesions from the infection on the inoculated leaves were recorded. The induction activity was evaluated using the antibacterial inhibition ratio, which was calculated by the average number of the lesions on the inoculated leaves with the corresponding control according to eq 1.

$$X\% = \frac{CK - T}{CK} \times 100 \quad (1)$$

where X is the antimicrobial inhibition ratio, *CK* is the average number of lesions on the control leaf, and *T* is the average number of lesions on the treated leaf.

Pyricularia oryzae. Rice seedlings at 2−3 leaf stage were treated with test compounds for 4 times as described above, then the plant was inoculated with the conidial suspension (10^5 spores/mL), and maintained in a dew chamber with 100% humidity for 7 days at 25 °C. The lesions on the inoculated leaves were recorded, and the induction activity was evaluated using the antifungal inhibition ratio, which was calculated by the average number of the lesions on the inoculated leaves with the corresponding control according to eq 1 as described above.

Bipolaris maydis. Maize seedlings at 1 leaf stage were treated with test compounds for 4 times as described above, then the plant was inoculated with the conidial suspension (10^5 spores/mL) and maintained in a dew chamber with 100% humidity for 7 days at 25 °C. The lesions on the inoculated leaves were recorded, and the induction activity was evaluated using the antifungal inhibition ratio, which was calculated by the average number of the lesions on the inoculated leaves with the corresponding control according to eq 1.

Colletotrichum lagenarium. Cucumber seedlings at a cotyledonary leaf stage were treated with test compounds for 4 times as described above, then the plant was inoculated with the conidial suspension (10^5 spores/mL) and maintained shaded in a dew chamber for 7 days at 25 °C. The lesions on the inoculated leaves were recorded, and the induction activity was evaluated using the antifungal inhibition ratio, which was calculated by the average number of lesions on the inoculated leaves with the corresponding control according to eq 1.

Erysiphe cichoracearum. Cucumber seedlings at a cotyledonary leaf stage were treated with test compounds for 4 times as described above, then the plant was inoculated with the conidial suspension (10^5 spores/mL) and maintained in a greenhouse with 100% humidity for 7 days at 25 °C. The lesions on the inoculated leaves were recorded, and the induction activity was evaluated using the antifungal inhibition ratio, which was calculated by the average number of lesions on the inoculated leaves with the corresponding control according to eq 1.

Second Assay Screening. The microorganisms used in the second assay screening include *P. oryzae*, *C. lagenarium*, *E. cichoracearum*, and the bacterium *X. oryzae*. All compounds were tested with two concentrations separately, 50 mg/L and 100 mg/L, for *E. cichoracearum* and *C. lagenarium*, while concentrations of 100 mg/L and 200 mg/L were used for *P. oryzae* and *X. oryzae*, respectively. The systemic acquired resistance activity of each test compound was measured using the backward method: plants were treated with test compounds for four times separately at 7, 5, 3, and 1 day before inoculation. After inoculation, the plants were cultured for 7 days, and the lesions on the inoculated leaves were recorded. Three repeated tests were performed for each compound. In every repeated test, five plants were used for the test of each compound. Double-distilled water and commercially available BTH (Actigard 50WG) were used as CK and positive control, as the commercialized plant activator BTH (Actigard 50WG) has been reported to induce SAR in different crops against a number of pathogens.[21] Determination of SAR activity of the tested compounds against the microorganisms was conducted according to the procedures described in the first assay screening.

Field Test. Compounds **3d** and **3e** were chosen to evaluate their activity against *Pseudoperonospora cubensis* and *Erysiphe cichoracearum* on cucumber (*Cucumis sativus* L.). Three concentrations, 500 mg/L, 250 mg/L, and 100 mg/L, were used for compounds **3d** and **3e**, with 250 mg/L of **3c** (BTH) and distilled water for positive control and CK. Additionally, commercial 50% Dimethomorph (WP) and 12.5% Myclobutanil (EC) were used as positive control against *Pseudoperonospora cubensis* and *Erysiphe cichoracearum* respectively in the field test to evaluate the efficiency of the novel compounds. The test was conducted in an experimental field in vegetable sheds, which were divided into subareas of 14 m^2, and within each subarea, 28 cucumber plants were planted. Test compounds were dissolved in acetone and diluted with water to the desired concentrations and sprayed on the two sides of the cucumber leaves evenly. First application was conducted right after field planting, and afterward, another two applications were conducted every 7 days. The inoculations were conducted 3 days after the last application of test compounds. Then the plants were cultured in sheds under natural temperature without manual control. Four repeated tests were performed for each test. In all repeated tests, the experiments were arranged in random. After the disease conditions became stable, the lesions on the plant leaves were recorded. The disease index and inhibition rate were calculated as follows. From every subarea, 10 plants were chosen, and their leaves were investigated and classified into different levels according to the following standards:

(1) no lesion;
(2) lesions occupying less than 5% of the leaf area;
(3) lesions occupying 6%−10% of the leaf area;
(4) lesions occupying 11%−25% of the leaf area;
(5) lesions occupying 26%−50% of the leaf area; and
(6) lesions occupying more than 50% of the leaf area.

The disease index and the inhibition efficiency were calculated according to eqs 2 and 3, respectively.

$$I = \frac{\sum (Y \times C)}{N \times 9} \times 100 \quad (2)$$

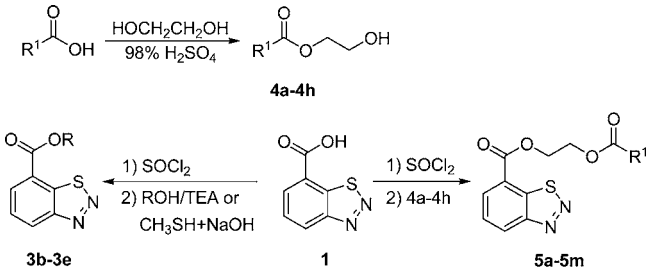
$$\text{Effeciency} = \frac{I_c - I_a}{I_c} \quad (3)$$

where *I* is the disease index, *Y* is the leaf number of a certain class, *C* is the corresponding lesion level, and *N* is the total leaf number of all levels. I_c is the disease index of CK plants, and I_a is the disease index of plants with test compound application.

RESULTS AND DISCUSSION

Preparation of Benzo-1,2,3-thiadiazole-7-carboxylate Derivatives. The general method for the preparation of the target compounds is shown in Scheme 1 and was previously described in the literature.[17] Also, the physical properties and structural data of compounds **3b**−**3e** and **5a**−**5d** were reported in our previous work.[17] Compounds **5e**−**5m** were synthesized according to the literature.[22,23] All compounds were

Scheme 1



3b	OR=OCH_3	5c	R^1=2-ClC_6H_4	5i	R^1=4-ClC_6H_4
3c	OR=SCH_3	5d	R^1=2-OHC_6H_4	5j	R^1=4-$O_2NC_6H_4$
3d	OR=OCH_2CF_3	5e	R^1=2-FC_6H_4	5k	R^1=C_6H_4CH=CH
3e	OR=$OCH_2CF_2CF_3$	5f	R^1=2-BrC_6H_4	5l	R^1=2-$CH_3OC_6H_4$
5a	R^1=C_6H_5	5g	R^1=2-IC_6H_4	5m	R^1=2,4-$Cl_2C_6H_3OCH_2$
5b	R^1=C_6F_5	5h	R^1=4-FC_6H_4		

separated and purified by recrystallization or silica gel chromatography, and their structures were determined by ^{1}H NMR, IR, elemental analyses, and HRMS or MS. Data of all target compounds are shown in Tables 1 and 2.

Biological Assay Activity. Plant activator is a novel kind of agrochemical that suggests an unusual mode of action on disease control by activating the defense system of plants. Therefore, it belongs to ecological agricultural pest protection products whose benefits are keeping the complicated and subtle balance among microorganisms in the environment because of their low toxicity and nonpollution. Antimicrobial activity screening in vitro showed that the novel compounds have nearly no direct antimicrobial activity against *P. oryzae*, *B. maydis*, *C. lagenarium*, and *X. oryzae*, as shown in Table 3.

Then, the compound induced SAR activities were screened. As can be seen in Table 4, compounds **3b**, **3c** (BTH), **3d**, and **3e** showed excellent activity on cucumber toward *E. cichoracearum* and *C. lagenarium*, all with inhibition rates above 98% at 7 days after inoculations. The change of ester group with a long chain ester generally reduced the activity, and only compounds **5a**, **5d**, and **5m** showed comparatively good activity, with inhibition rates of 97%, 89%, and 92% toward *E. cichoracearum*, and 96%, 99%, and 92% toward *C. lagenarium*, respectively. At the same time, **5f**, **5i**, and **5j** showed good activity toward *C. lagenarium*, with inhibition rates of 97%, 90%, and 92%, but only moderate inhibition rates were observed with *E. cichoracearum* (Table 4). However, while screening of the novel compounds on maize and rice toward *B. maydis*, *P. oryzae*, and *X. oryzae*, all compounds including **3c** (BTH) showed poor efficiency compared with the results on cucumber. As shown in Table 5, all compounds showed little activity on *B. maydis* of maize at 7 days after inoculation, which may have resulted from the variations of microbial strains. Higher efficiency was observed on *P. oryzae* and *X. oryzae* of rice, though not as good as the results on cucumber. Compounds with larger 7-carboxylate groups seemed to be more efficient toward the bacterium *X. oryzae* than those with smaller 7-carboxylate groups, as **5a**, **5d**, **5e**, **5f**, **5i**, **5j**, **5k**, and **5m** all showed inhibition rates of above 50% on *X. oryzae* of rice, and the best was **5f**, which showed an inhibition rate 92%, while for compounds with smaller 7-carboxylate groups, only fluoro-containing compound **3d** showed parallel effects on these two diseases but still not as good as compounds with larger 7-carboxylate groups such as **5m** (Table 5). According to the first screening on four fungi (*P. oryzae*, *B. maydis*, *C. lagenarium*, and *E. cichoracearum*) and one bacterium (*X. oryzae*), the compounds with smaller 7-carboxylate groups were generally more efficient toward the four fungi, while compounds with larger 7-carboxylate groups were more efficient toward the bacterium, for example, compounds **5d**, **5e**, **5f**, **5i**, and **5m** showed higher inhibition activities than all of the compounds with smaller 7-carboxylate groups toward *X. oryzae*, in our first screening. In combination with the fungicide screening results, the above data suggested that these compounds possessed characteristics of plant activators.

Comparatively high concentration was used in the first screening to avoid skipping potential active compounds, while some phytotoxicity was observed on the test plants. Therefore,

Table 3. Fungicide Activity of Benzo-1,2,3-thiadiazole-7-carboxylate Derivatives

	PO[a]		BM		CL		XO	
compd	*D*[b] (mm)	I.R.[b] (%)	*D* (mm)	I.R. (%)	*D* (mm)	I.R. (%)	*D* (mm)	I.R. (%)
3c (BTH)	8.0	11 ± 3	13	13 ± 5	16	6 ± 4	10	22 ± 1
3b	5.0	44 ± 5	12	20 ± 6	13	24 ± 3	6	50 ± 5
3d	11.0	0	14	6 ± 6	12	29 ± 5	12	4 ± 3
3e	10.0	0	14	6 ± 3	16	6 ± 2	13	0
5a	8.0	11 ± 1	13	13 ± 4	16	6 ± 3	11	8 ± 4
5b	7.0	22 ± 6	13	13 ± 5	14	18 ± 5	12	4 ± 3
5c	8.0	11 ± 5	14	7 ± 7	19	0	12	0
5d	9.0	0	12	20 ± 2	15	12 ± 1	12	0
5e	7.5	17 ± 4	13	13 ± 4	13	24 ± 2	12	0
5f	7.5	17 ± 5	14	7 ± 1	16	6 ± 5	11	8 ± 2
5g	9.0	0	13	13 ± 1	17	0	13	0
5h	8.0	11 ± 5	13	13 ± 3	16	6 ± 4	12	0
5i	7.0	23 ± 2	13	13 ± 4	14	18 ± 3	11	8 ± 1
5j	8.0	11 ± 5	13	13 ± 5	19	0	12	0
5k	9.5	0	13	13 ± 6	19	0	11	8 ± 4
5l	7.5	17 ± 5	13	13 ± 4	14	18 ± 5	11	8 ± 3
5m	9.0	0	12	20 ± 3	14	18 ± 5	12	0
CK[d]	9.0	ND[c]	15	ND	17	ND	12	ND

[a]Microorganisms used: PO, *Pyricularia oryzae*; BM, *Bipolaris maydis*; CL, *Colletotrichum lagenarium*; XO, *Xanthomonas oryzae*. [b]*D* = diameter of fungi spread; I.R. = inhibition rate. [c]ND = not detected. [d]Distilled water was used as CK.

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Table 4. Induction Activity of Novel Compounds on Cucumber in First Assay Screening

		EC[a] (%)				CL (%)			
compd	concn (mg/L)	1 d[b]	3 d	5 d	7 d	1 d	3 d	5 d	7 d
3c (BTH)	200	65 ± 5	88 ± 3	93 ± 3	100	29 ± 5	96 ± 1	100	100
3b	500	53 ± 5	86 ± 4	98	100	65 ± 4	88 ± 5	100	98
3d	500	76 ± 6	89 ± 5	85 ± 2	100	52 ± 5	87 ± 5	89 ± 3	99
3e	500	74 ± 7	90 ± 3	77 ± 4	99	52 ± 4	66 ± 4	80 ± 4	100
5a	500	61 ± 5	87 ± 4	96	97 ± 1	22 ± 2	92 ± 3	94 ± 1	96 ± 1
5b	500	61 ± 8	68 ± 5	70 ± 5	30 ± 2	31 ± 1	44 ± 6	76 ± 5	86 ± 6
5c	500	56 ± 5	72 ± 6	66 ± 4	32 ± 3	56 ± 6	58 ± 7	76 ± 5	83 ± 3
5d	500	68 ± 4	84 ± 6	76 ± 2	89 ± 2	63 ± 7	78 ± 5	84 ± 4	99
5e	500	46 ± 5	68 ± 7	76 ± 5	14 ± 5	51 ± 8	51 ± 6	56 ± 6	81 ± 3
5f	500	55 ± 4	71 ± 6	73 ± 3	72 ± 3	69 ± 7	63 ± 4	85 ± 5	97 ± 1
5g	500	53 ± 6	54 ± 8	71 ± 4	38 ± 4	60 ± 5	78 ± 2	58 ± 4	80 ± 7
5h	500	42 ± 4	75 ± 5	65 ± 3	62 ± 2	46 ± 4	79 ± 5	43 ± 3	86 ± 5
5i	500	55 ± 4	57 ± 3	60 ± 5	42 ± 2	74 ± 6	80 ± 5	46 ± 5	90 ± 3
5j	500	46 ± 3	55 ± 4	50 ± 2	43 ± 4	68 ± 5	82 ± 4	71 ± 6	92 ± 1
5k	500	64 ± 4	42 ± 5	26 ± 1	19 ± 5	78 ± 4	78 ± 3	51 ± 7	36 ± 5
5l	500	78 ± 5	38 ± 4	53 ± 6	65 ± 4	64 ± 5	76 ± 6	62 ± 6	86 ± 4
5m	500	56 ± 2	79 ± 6	90 ± 2	92 ± 1	14 ± 5	68 ± 5	ND[c]	92 ± 2

[a]Fungi used: EC, *Erysiphe cichoracearum*; CL, *Colletotrichum lagenarium*. [b]Induction activities were evaluated separately at 1 day, 3 days, 5 days, and 7 days after inoculation. [c]ND = not detected.

Table 5. Induction Activity of Novel Compounds on Maize and Rice in First Assay Screening

		BM[a] (%)				PO (%)				XO (%)			
compd	concn (mg/L)	1 d[b]	3 d	5 d	7 d	1 d	3 d	5 d	7 d	1 d	3 d	5 d	7 d
3c(BTH)	200	10 ± 4	31 ± 3	32 ± 3	31 ± 5	42 ± 3	58 ± 3	67 ± 2	63 ± 2	36 ± 3	14 ± 4	37 ± 3	31 ± 3
3b	500	9 ± 3	19 ± 4	21 ± 3	10 ± 3	54 ± 5	48 ± 5	29 ± 3	52 ± 2	35 ± 3	49 ± 5	57 ± 3	42 ± 5
3d	500	8 ± 1	17 ± 4	24 ± 4	22 ± 3	44 ± 6	49 ± 5	45 ± 4	57 ± 4	21 ± 5	23 ± 5	39 ± 5	56 ± 5
3e	500	8 ± 2	22 ± 4	19 ± 3	30 ± 5	39 ± 5	47 ± 4	44 ± 5	68 ± 4	21 ± 4	49 ± 4	45 ± 5	41 ± 5
5a	500	1	5 ± 3	13 ± 3	21 ± 4	29 ± 3	54 ± 6	57 ± 6	63 ± 5	19 ± 4	50 ± 5	56 ± 3	53 ± 3
5b	500	18 ± 3	18 ± 2	16 ± 4	32 ± 4	30 ± 1	47 ± 5	59 ± 6	57 ± 3	22 ± 2	31 ± 3	33 ± 4	28 ± 4
5c	500	4 ± 1	5 ± 1	18 ± 4	25 ± 5	32 ± 2	38 ± 4	43 ± 3	50 ± 4	8 ± 4	47 ± 4	66 ± 5	38 ± 6
5d	500	29 ± 2	22 ± 3	27 ± 2	24 ± 6	65 ± 3	59 ± 5	39 ± 2	51 ± 4	17 ± 1	71 ± 6	87 ± 3	57 ± 4
5e	500	10 ± 2	8 ± 3	24 ± 5	21 ± 4	34 ± 4	37 ± 3	42 ± 3	47 ± 2	13 ± 3	52 ± 5	59 ± 2	58 ± 7
5f	500	20 ± 4	14 ± 2	33 ± 4	32 ± 5	70 ± 5	37 ± 3	50 ± 3	49 ± 5	40 ± 4	20 ± 7	54 ± 3	92 ± 3
5g	500	18 ± 3	3 ± 2	24 ± 3	24 ± 4	77 ± 7	62 ± 6	60 ± 4	60 ± 6	17 ± 4	53 ± 6	45 ± 5	46 ± 5
5h	500	24 ± 4	10 ± 3	23 ± 6	40 ± 5	56 ± 3	59 ± 3	44 ± 3	42 ± 5	1	41 ± 5	34 ± 5	47 ± 5
5i	500	13 ± 3	5 ± 2	19 ± 2	17 ± 4	85 ± 4	83 ± 5	62 ± 5	63 ± 5	30 ± 3	53 ± 6	36 ± 5	59 ± 4
5j	500	6 ± 4	6 ± 3	30 ± 7	30 ± 5	89 ± 6	66 ± 6	60 ± 3	66 ± 3	46 ± 4	49 ± 6	25 ± 3	55 ± 6
5k	500	22 ± 4	13 ± 2	19 ± 3	15 ± 3	59 ± 6	71 ± 4	29 ± 2	71 ± 4	17 ± 5	28 ± 5	34 ± 4	52 ± 3
5l	500	33 ± 4	17 ± 3	29 ± 5	24 ± 4	68 ± 5	70 ± 5	49 ± 3	60 ± 5	26 ± 3	58 ± 5	49 ± 4	40 ± 3
5m	500	14 ± 3	18 ± 4	21 ± 4	24 ± 3	40 ± 6	91 ± 2	54 ± 3	75 ± 2	31 ± 2	36 ± 4	50 ± 2	74 ± 4

[a]Microorganisms used: BM, *Bipolaris maydis*; PO, *Pyricularia oryzae*; XO, *Xanthomonas oryzae*. [b]Induction activities were evaluated separately at 1 day, 3 days, 5 days, and 7 days after inoculation.

lower concentration of active compounds should be further screened to evaluate their efficiency.

In the second screening, compounds **3b**, **3d**, **3e**, **5a**, **5d**, and **5m** were chosen to evaluate their disease defense efficiency (Tables 6 and 7). Under screening concentration (50 mg/L and 100 mg/L), most compounds showed excellent activity against *C. lagenarium* (Table 6), with inhibition rates above 90% at 7 days after inoculation except for **5d**. However, comparatively lower activity was observed on *E. cichoracearum*, with the highest inhibition rate of 82% shown by 100 mg/L of **3e**, and 100 mg/L of test compounds had much higher activity than those of 50 mg/L. Higher concentration (100 mg/L and 200 mg/L for *P. oryzae* and 100 mg/L for *X. oryzae*) were applied in the screening against *X. oryzae* and *P. oryzae*, as shown in Table 7. The results illustrated that compounds **3b**, **3d**, and **3e** had good activity toward the fungi at test concentrations, with inhibition rates of all above 50%. In summary of the first and the second screening, most testing compounds showed good resistance inducing activities and compounds with smaller 7-carboxylate groups (**3b**−**3e**) were generally more efficient than those with larger 7-carboxylate groups (**5a**−**5m**). Overall, compounds 2,2,2-trifluoroethtyl benzo[1,2,3]thiadiazole-7-carboxylate (**3d**) and 3,3,3,2,2-pentafluoropropyl benzo[1,2,3]thiadiazole-7-carboxylate (**3e**) stood out with comparatively higher activity than other tested compounds, probably caused by the fluorine atoms in these

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Table 6. Induction Activity of Novel Compounds on Cucumber in Second Assay Screening

		CL[a] (%)				EC (%)			
compd	concn (mg/L)	1 d[b]	3 d	5 d	7 d	1 d	3 d	5 d	7 d
3b	50	73 ± 6	85 ± 3	90 ± 6	95 ± 1	12 ± 2	42 ± 3	53 ± 5	48 ± 6
	100	79 ± 4	89 ± 4	93 ± 2	97 ± 1	35 ± 3	42 ± 4	63 ± 3	75 ± 3
3d	50	37 ± 3	88 ± 3	82 ± 3	95 ± 2	11 ± 2	17 ± 3	45 ± 4	34 ± 5
	100	77 ± 4	91 ± 2	88 ± 2	98	58 ± 3	56 ± 6	57 ± 3	64 ± 3
3e	50	42 ± 2	89 ± 6	79 ± 6	99	28 ± 2	72 ± 3	62 ± 4	63 ± 4
	100	60 ± 3	89 ± 4	77 ± 4	99	35 ± 6	77 ± 4	81 ± 7	82 ± 5
5a	50	61 ± 3	60 ± 3	34 ± 3	89 ± 6	6 ± 1	28 ± 2	21 ± 6	32 ± 3
	100	86 ± 6	64 ± 3	83 ± 2	98	31 ± 3	67 ± 5	11 ± 2	78 ± 4
5d	50	40 ± 4	51 ± 2	23 ± 3	79 ± 2	15 ± 2	47 ± 6	51 ± 4	34 ± 6
	100	37 ± 3	87 ± 6	72 ± 6	73 ± 6	29 ± 6	37 ± 9	79 ± 6	44 ± 5
5m	50	27 ± 1	63 ± 4	76 ± 7	91 ± 4	0	41 ± 6	35 ± 6	48 ± 2
	100	58 ± 2	84 ± 3	90 ± 3	97 ± 1	32 ± 1	74 ± 6	52 ± 4	68 ± 3
BTH (50WG)	50	58 ± 3	84 ± 4	100	100	82 ± 6	90 ± 5	91 ± 3	72 ± 4
	100	66 ± 4	96 ± 3	100	100	93 ± 3	98	95 ± 1	94 ± 1

[a]Fungi used: CL, *Colletotrichum lagenarium*; EC, *Erysiphe cichoracearum*. [b]Induction activities were evaluated separately at 1 day, 3 days, 5 days, and 7 days after inoculation.

Table 7. Induction Activity of Novel Compounds on Rice in Second Assay Screening

		XO[a] (%)				PO (%)			
compd	concn (mg/L)	1 d[b]	3 d	5 d	7 d	1 d	3 d	5 d	7 d
3b	100	ND[c]	ND	ND	ND	50 ± 5	67 ± 6	58 ± 4	79 ± 5
	200	33 ± 2	16 ± 2	35 ± 3	57 ± 6	53 ± 4	73 ± 2	83 ± 1	79 ± 3
3d	100	ND	ND	ND	ND	50 ± 5	67 ± 4	83 ± 5	79 ± 5
	200	0	29 ± 2	30 ± 3	55	54 ± 3	78 ± 2	67 ± 3	79 ± 4
3e	100	ND	ND	ND	ND	50 ± 2	57 ± 4	67 ± 3	64 ± 6
	200	64 ± 4	63 ± 5	48 ± 5	73 ± 6	50 ± 4	68 ± 4	75 ± 5	74 ± 5
5a	100	ND	ND	ND	ND	0	56 ± 4	67 ± 4	68 ± 5
	200	54 ± 4	28 ± 3	44 ± 4	48 ± 5	50 ± 6	67 ± 3	75 ± 4	76 ± 6
5d	100	ND	ND	ND	ND	62 ± 4	11 ± 2	83 ± 6	64 ± 5
	200	56 ± 4	40	8 ± 2	15 ± 6	50 ± 5	56 ± 3	92 ± 6	57 ± 5
5m	100	ND	ND	ND	ND	50 ± 6	44 ± 5	67 ± 5	ND
	200	50 ± 4	60 ± 4	8 ± 3	0	62 ± 4	67 ± 5	83 ± 4	72 ± 3
BTH (50WG)	100	ND	ND	ND	ND	86 ± 5	84 ± 6	94 ± 5	77 ± 4
	200	76 ± 4	63 ± 3	95 ± 4	100	85 ± 6	94 ± 3	95 ± 3	96 ± 2

[a]Microorganisms used: XO, *Xanthomonas oryzae*; PO, *Pyricularia oryzae*. [b]Induction activities were evaluated separately at 1 day, 3 days, 5 days, and 7 days after inoculation. [c]ND = not detected.

two compounds as a result of the special properties of fluorine atoms in the process of absorption and metabolism,[24] and further, these two compounds were more facile in synthesis than **3c** (BTH) in our laboratory, so it is highly significant to further evaluate their activities and applications in agriculture.

To develop novel plant activators appropriate for agricultural application, the candidate compounds must possess broad-spectrum and high activities against common diseases, and they must be facile in preparation with low cost as well. Hereby, **3d** and **3e** were chosen for the field test to further confirm their activities and potential application as novel plant activators using *Pseudoperonospora cubensis* and *Erysiphe cichoracearum* on cucumber (*Cucumis sativus* L.). As shown in Table 8, compounds **3d** and **3e** showed good activity against *P. cubensis*, with average efficiencies higher than that of the positive control **3c** (BTH) in all four tests in different locations when tested under the same concentration 250 mg/L. As for *E. cichoracearum*, the two compounds showed even higher inhibition efficiency of more than 90% at test concentrations, and also compound **3c** showed an efficiency of 90% at 250 mg/L in test location 1, Beijing, which can be seen in Table 8. The test results in the other three locations showed that compounds **3d** and **3e** had parallel activity against *E. cichoracearum*, except in location 2, where compound **3e** seemed less effective than **3d** and **3c**, but that might be a sporadic case as test results in other locations were consistent and showed good activities. Generally, compounds **3d** and **3e** were more potent than the positive control **3c** (BTH) at the same concentration of 250 mg/L and even showed higher efficiency than another positive control, the commercial bactericide 12.5% Myclobutanil (EC) toward *E. cichoracearum* in some cases. Additionally, it can be seen from Table 8 that the potency did not increase obviously with the increase of the compound concentration; therefore, a concentration of 100−200 mg/L was most appropriate for the compounds. The field tests were conducted in four locations during two years, and the test results displayed good repeatability across most locations, as can be seen in Table 8.

In this work, a series of benzo-1,2,3-thiadiazole-7-carboxylate derivatives were synthesized, and their induction activities as plant activators were evaluated. Compounds **3d** and **3e** showed

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Table 8. Field Test Results of 3d and 3e against *Erysiphe cichoracearum* and *Pseudoperonospora cubensis*[a]

		efficiency[b](%)							
		Pseudoperonospora cubensis				*Erysiphe cichoracearum*			
compd	concn (mg/L)	1	2	3	4	1	2	3	4
3d	500	76 ± 3	80 ± 4	77 ± 3	80 ± 5	94 ± 5	82 ± 4	83 ± 4	83 ± 3
	250	68 ± 4	78 ± 4	71 ± 4	70 ± 4	92 ± 4	78 ± 5	82 ± 5	68 ± 4
	100	67 ± 2	78 ± 4	63 ± 2	60 ± 3	92 ± 3	76 ± 4	81 ± 3	60 ± 4
3e	500	74 ± 4	85 ± 3	80 ± 4	84 ± 4	96 ± 3	55 ± 3	90 ± 5	74 ± 4
	250	71 ± 4	81 ± 3	72 ± 3	75 ± 3	94 ± 5	52 ± 3	90 ± 4	64 ± 4
	100	71 ± 3	63 ± 2	67 ± 3	59 ± 3	87 ± 4	44 ± 3	77 ± 4	53 ± 3
3c	250	67 ± 3	63 ± 3	62 ± 3	64 ± 4	90 ± 5	80 ± 4	84 ± 4	68 ± 3
solvent	ND[c]	13 ± 1	−2 ± 2	2 ± 1	8 ± 3	12 ± 3	ND	17 ± 3	10 ± 2
12.5% Myclobutanil (EC)	500	86 ± 3	ND	88 ± 3	88 ± 4	88 ± 5	77 ± 3	71 ± 3	84 ± 4

[a]Field tests were conducted in four locations including two sites, **1** and **2**, in Beijing with the natural temperatures between 20−30 °C (2008, Spring) and 18−26 °C (2008, Autumn), respectively; site **3** in Liaoning Province with the natural temperature between 18−27 °C (2009, Autumn); and site **4** in Shandong Province with the natural temperature between 21−30 °C (2009, Spring). [b]Efficiency is the average of all repeated tests. [c]ND = not detected.

higher activity than other compounds toward the test diseases. It should be noted that such esters are readily hydrolyzed during or just after uptake by the plant material, in the apoplastic space, so the efficiency of these compounds as SAR inducers is probably caused by the free acid. However, the free acid of BTH showed very low activity in vivo, and the modification on the 7-carboxy group with certain esters as BTH greatly improved the activity, probably by improving the liposolubility of free acid.[11] In the same way, the introduction of other particular groups such as fluorine-containing groups may also alter the nature of the compounds due to the special properties of fluorine atoms. As a result, higher efficiency of the fluorine-containing esters might have some advantages in penetration rates into plants or resistance to hydrolysis during their absorption. Furthermore, the field test illustrated that **3d** and **3e** were more potent than the commercialized plant activator BTH (**3c**) against *P. cubensis* and *E. cichoracearum*. Importantly, the preparation of compound **3d** is more facile and with lower cost than BTH. Our in-progress synthesizing work illustrated that the last step yield of **3d** from relevant acid was as high as 96%, in comparison with a yield of less than 60% for **3c** (BTH) in our laboratory. The results of field tests from four locations over a period of two years were consistent (Table 8). These promising results indicated that compound **3d** was a potent plant activator for agricultural applications and is being developed for future commercialization.

AUTHOR INFORMATION

Corresponding Author

*Tel: 86-21-64251399; Fax: 86-21-64252603. E-mail: zhjzhao@ecust.edu.cn(Z.Z.); yfxu@ecust.edu.cn (Y.X.).

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