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Synthesis and Fungicidal Activity of Aryl Carbamic Acid-5-aryl-2-furanmethyl Ester

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Chitin, a major structural component of insect cuticle and fungus cell wall but absent in plants and vertebrates, is regarded as a safe and selective target for pest control agents. Chitin synthesis inhibitors (CSIs) have been well-known as insect growth regulators (IGRs) but rarely found as fungicides in agriculture. To find novel CSIs with good activity, benzoylphenylurea, a typical kind of CSIs, was chosen as the lead compound and 26 novel aryl carbamic acid-5-aryl-2-furanmethyl esters were designed by converting the urea linkages of benzoylphenylureas to carbamic acid esters and changing the aniline parts into furanmethyl groups. The title compounds were synthesized and their structures confirmed by IR, ^{1}H NMR, and elemental analysis. Preliminary insecticidal and fungicidal bioassays were carried out. The results indicated that the title compounds had no insecticidal effect on *Culex pipiens pallens* and *Plutella xylostella Linnaeus*, but most compounds exhibited good fungicidal activities against *Corynespora cassiicola*, *Thanatephorus cucumeris*, *Botrytis cinerea*, and *Fusarium oxysporum*. In particular, compounds **V-4**, **V-6**, **V-7**, and **V-8** showed better activities against the four strains than those of the commercialized fungicides. The morphologic result suggested that compound **V-21** had disturbed the cell wall formation of *C. cassiicola*. The results indicated that modification on the urea linkage of benzoylphenylurea was an effective way to discover new candidates for fungicides.

KEYWORDS: Chitin synthesis inhibitors; benzoylphenylureas; carbamic acid ester; synthesis; fungicidal activity

INTRODUCTION

Chitin, the β-(1→4)-linked homopolymer of *N*-acetyl-D-glucosamine, is a major structural component of insect cuticles and fungus cell walls but absent in plants and vertebrates. This taxonomic difference provides the rationale for considering chitin as a safe and selective target for pest control agents (*1*, *2*). Chitin synthesis inhibitors (CSIs), which can disrupt the formation of chitin, will affect the normal growth and development of insects and fungi but have no effect on vertebrates and plants. CSIs play an important role in integrated pest management (IPM). Therefore, to find new CSIs it is necessary to meet the requirement of various pest managements in sustainable agriculture (*3*, *4*).

Benzoylphenylureas (BPUs), first discovered in the 1970s, are a typical kind of CSI (*5*, *6*). BPUs have attracted considerable attention for decades because of their unique mode of action coupled with high activities on targeted pests and low toxicity to nontarget organisms (*5*−*17*). Their general structures **A** consist of three parts including the benzoyl (X), the urea linkage (Y), and the aniline (Z) (*9*). During the past three decades, many modifications on the benzoyl (X) and aniline (Z) parts led to the discoveries of many commercial insecticides, such as diflubenzuron, chlorfluazuron, teflubenzuron, bistrifluoron, and noviflumuron (*9*−*13*). However, modification on the urea linkage (Y) was less considered, but some efforts on this part have been made. For example, Grosscurt found that the compounds had good insecticidal properties when the urea linkage was converted into carbamoyl-2-pyrazolines (*14*). Chen reported that the substitution of the hydrogen on the nitrogen atom of urea linkage with carbamylosulfenyl or formate could retain the insecticidal activity (*15*−*17*).

In our previous work, the benzoyl (X) part was modified with a furoyl group to get benzoylureas **B** (*20*), and the aniline (Z) part was replaced with a furoyl group to obtain dibenzoylureas **C** (*18*, *19*). Their bioassay results indicated that some compounds also had certain insecticidal activity. In the present work, an effort of structure optimization was carried out, in which the urea linkage was converted to carbamic acid ester by replacing NH with O, whereas the aniline part was replaced with a furanmethyl group (**Scheme 1**). Twenty-six novel aryl carbamic acid-5-aryl-2-furanmethyl esters (**V**) were designed and synthesized for the purpose of new pesticide discovery. Their insecticidal activities in vivo and fungicidal activities in vitro were evaluated preliminarily.

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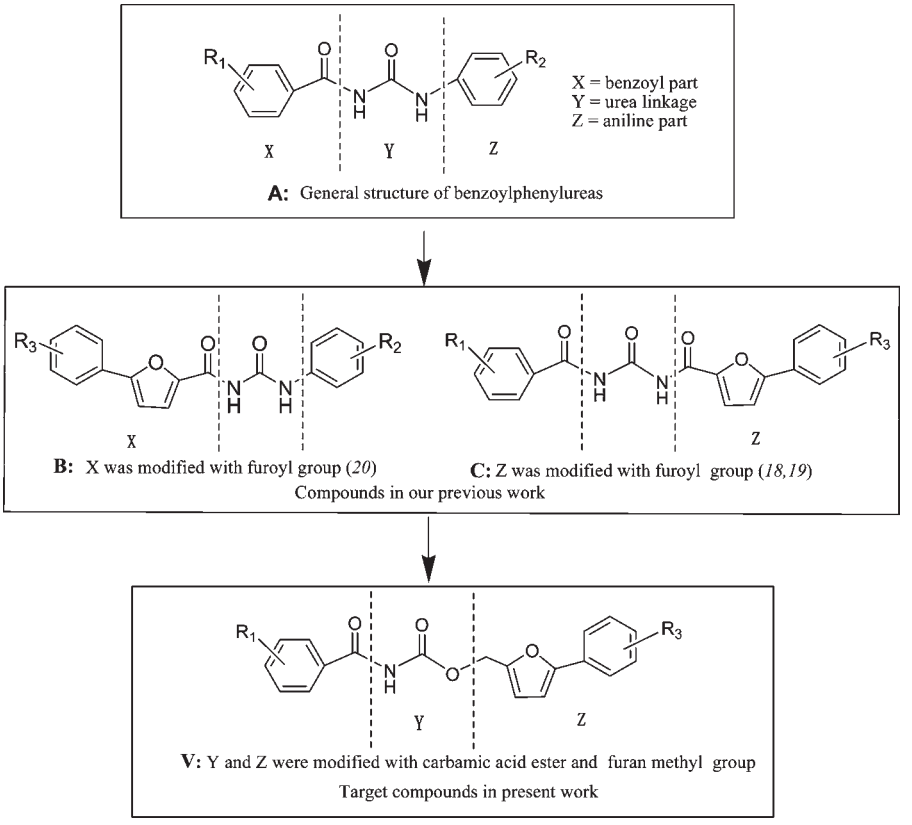
Scheme 1. Design Strategy for Target Compounds **V**



Furthermore, a morphological study on the cell wall formation of *Corynespora cassiicola* was done primarily to identify whether the formation of chitin had been disrupted or not.

MATERIALS AND METHODS

Instruments and Reagents. Melting points were measured on a Cole-Parmer melting point apparatus, and the thermometer was uncorrected. ^{1}H NMR spectra were obtained in deuterochloroform or hexadeuterodimethyl sulfoxide using a Bruker Advance DPX (300 MHz) (Switzerland) with tetramethylsilane as internal standard. Elemental analysis was performed on an ST-Carlo Erba Flash EA 1112 elemental analyzer by the Analytical Center of the Institute of Chemistry, Chinese Academy of Science. Infrared spectra (ν_{max} in cm^{-1}) were recorded on a Shimadzu IR-435 apparatus. The solvents and reagents were mainly purchased from the Beijing Chemical Reagents Co., People's Republic of China.

Chemical Synthesis. *General Procedure for the Synthesis of Compounds 5-Aryl-2-furanmethanol* (***II***). Compounds **II** were prepared from compound **I** with $NaBH_4$ as the reductant (*21*), and **I** was synthesized from substituted aniline by Meerwein arylation reaction using the reported procedure (*22*).

General Procedure for the Synthesis of Substituted Benzoyl Isocyanate (***IV***). Compounds **IV** were obtained through the reaction of corresponding benzamides **III** and oxalyl dichloride according to the literature (*23*).

General Procedure for the Synthesis of the Target Compound ***V*-26**. Into a solution of 5-(4-bromophenyl)-2-furanmethanol (1.5 g, 0.006 mol) dissolved in 30 mL of purified toluene was added 2-chlorobenzoyl isocyanate (1.29 g, 0.007 mol). The reaction mixture was stirred at room temperature for 0.5 h. The solvent was filtered off. The solid was dried and then recrystallized from the mixture solvent of petroleum ether and ethyl acetate ($V_{\text{petroleum ether}}/V_{\text{ethyl acetate}}$ = 2.5:1). A white solid (**V-26**, 184 g) was obtained in 71.4% yield: mp 114−116 °C; ^{1}H NMR (300 MHz) δ 11.37 (s, 1H, NH), 7.61−7.68 (m, 4H, ArH-Fu), 7.36−7.50 (m, 4H, ArH), 7.03 (d, J = 3.39 Hz, 1H, FuH), 6.69 (d, J = 3.39 Hz, 1H, FuH), 5.17 (s, 2H, CH_2); IR, ν 3200, 1770, 1690, 1510, 1480, 1220, 1040 cm^{-1}. Anal. Calcd for $C_{19}H_{13}BrClNO_4$: C, 52.50; H, 3.01; N, 3.22. Found: C, 52.46; H, 3.01; N, 3.35.

All other title compounds were prepared according to the same procedure as compound **V-26**. The data of their yields, melting points, and elemental analyses are listed in **Table 1** and the data of ^{1}H NMR and IR are listed in **Table 2**.

Biological Assays. *Insecticidal Activity*

(*a*) *Insecticidal Activity against Plutella xylostella Linnaeus*. Insecticidal activities against *P. xylostella* Linnaeus were evaluated using the immersion method (*24*). *P. xylostella* Linnaeus was maintained in the Institute of Plant Protection, Chinese Academy of Agricultural Science. Test solutions were made by dissolving the title compounds in a mixture solvent of acetone and methanol ($V_{\text{acetone}}/V_{\text{methanol}}$ = 1:1), adding a little 0.1% Tween-80 as the emulsifier, and then diluting to 600 mg L^{-1} with water. The insects were raised at 27 ± 1 °C, with a 12:12 h (light/dark) photoperiod and 80% relative humidity. The results were observed after 72 h and expressed by death percentage. The mixture solvent of acetone and methanol was set as blank control, and 87% fipronil was set as insecticidal control. Three replicates were performed.

(*b*) *Larvicidal Activity against Mosquito* (*Culex pipiens pallens*). Larvicidal activities of the target compounds **V** against mosquitoes were evaluated by using the reported procedure (*16*). Compounds **V** were dissolved in acetone and distilled water at a terminal concentration of 2000 mg L^{-1}. Then 20 fourth-instar mosquito larvae were put into 10 mL of the tested solution and raised for 8 days. The results were expressed by death percentage. **RH-5849** and acetone were set as insecticidal and blank control. They were tested under the same condition as **V**. Four replicates were performed.

Fungicidal Activity. The preliminary fungicidal activities in vitro were tested against four kinds of strains: *Botrytis cinerea*, *Corynespora cassiicola*, *Fusarium oxysporum*, and *Thanatephorus cucumeris*. All of the strains were conserved in the Institute of Vegetable and Flowers, Chinese Academy of Agricultural Science. Commercialized fungicides, 75% chlorothalonil WP, 3% jingangmycin AS, 40% pyrimethanil SC, and 70% thiophanate-methyl WP were set as control for the above four strains, respectively.

The fungicidal activities of the title compounds **V** against above four strains in vitro were evaluated using the mycelium growth rate test (*25*).

Table 1. Physical and Elemental Data of Compounds **V**

					elemental analysis		
compd	R_1	R_3	mp (°C)	yield (%)	C (calcd)	H (calcd)	N (calcd)
V-1	2,6-F_2	2-F	114−116	77.3	60.99 (60.81)	3.32 (3.22)	3.65 (3.73)
V-2	2,6-F_2	3-F	118−119	78.6	60.60 (60.81)	3.22 (3.22)	3.90 (3.73)
V-3	2,6-F_2	4-F	131−133	73.5	60.78 (60.81)	3.33 (3.22)	3.94 (3.73)
V-4	2,6-F_2	2,4-F_2	120−121	52.4	57.90 (58.02)	2.97 (2.82)	3.74 (3.56)
V-5	2,6-F_2	2-Cl	122−124	41.5	58.16 (58.25)	3.16 (3.09)	3.58 (3.58)
V-6	2,6-F_2	3-Cl	123−125	50.8	58.09 (58.25)	3.28 (3.09)	3.82 (3.58)
V-7	2,6-F_2	4-Cl	121−122	48.6	58.21 (58.25)	3.14 (3.09)	3.75 (3.58)
V-8	2,6-F_2	2-Br	117−118	53.4	52.47 (52.32)	2.94 (2.77)	3.47 (3.21)
V-9	2,6-F_2	4-Br	124−126	61.5	52.28 (52.32)	2.83 (2.77)	3.34 (3.21)
V-10	2,6-Cl_2	2-F	145−147	75.9	55.74 (55.90)	2.98 (2.96)	3.18 (3.43)
V-11	2,6-Cl_2	3-F	147−149	71.8	55.85 (55.90)	3.10 (2.96)	3.55 (3.43)
V-12	2,6-Cl_2	4-F	133−135	75.6	55.96 (55.90)	2.99 (2.96)	3.56 (3.43)
V-13	2,6-Cl_2	2,4-F_2	147−149	78.9	53.56 (53.54)	2.80 (2.60)	3.44 (3.29)
V-14	2,6-Cl_2	2-Cl	146−148	88.4	53.68 (53.74)	2.91 (2.85)	3.48 (3.30)
V-15	2,6-Cl_2	3-Cl	150−152	64.2	53.66 (53.74)	2.98 (2.85)	3.26 (3.30)
V-16	2,6-Cl_2	4-Cl	146−148	83.5	53.92 (53.74)	2.91 (2.85)	3.48 (3.30)
V-17	2,6-Cl_2	2-Br	145−146	83.1	48.51 (48.65)	2.70 (2.58)	2.98 (2.99)
V-18	2,6-Cl_2	4-Br	135−137	70.5	48.92 (48.65)	2.65 (2.58)	3.24 (2.99)
V-19	2-Cl	2-F	123−124	68.2	61.03 (61.06)	3.69 (3.51)	3.82 (3.75)
V-20	2-Cl	3-F	129−131	51.1	61.35 (61.06)	3.52 (3.51)	3.81 (3.75)
V-21	2-Cl	4-F	131−133	83.6	60.80 (61.06)	3.54 (3.51)	3.94 (3.75)
V-22	2-Cl	2-Cl	105−106	36.4	58.26 (58.48)	3.34 (3.36)	3.71 (3.59)
V-23	2-Cl	3-Cl	138−139	70.6	58.31 (58.48)	3.43 (3.36)	3.70 (3.59)
V-24	2-Cl	4-Cl	143−144	88.7	58.28 (58.48)	3.36 (3.36)	3.80 (3.59)
V-25	2-Cl	2-Br	106−107	74.1	52.64 (52.50)	2.98 (3.01)	3.33 (3.22)
V-26	2-Cl	4-Br	143−144	71.4	52.46 (52.50)	3.01 (3.01)	3.35 (3.22)

Both control fungicides and synthesized compounds were dissolved in DMF at the concentration of 50 mg L^{-1}. The culture media were obtained by mixing the solution of compounds **V** in DMF with potato dextrose agar (PDA), on which fungus cakes were placed. The blank test was made using DMF. The culture had been stored in an incubator at 24 ± 0.5 °C for 2 days. Three replicates were performed. After the mycelia grew completely, the diameters of the mycelia were measured and the inhibitory rates were calculated according to the formula

$$I\,(\%) = \frac{C-T}{C} \times 100\%$$

in which I stands for the inhibition (%), C for the diameter of mycelia in the blank control test (in mm), and T for the diameter of mycelia in the presence of compounds **V** (in mm). The results are shown in **Table 5**.

Morphological Study on Cell Wall of Fungus. *C. cassiicola* was taken as test fungus, **V-21** was selected as test compound, and thiophanate methyl (TM) was chosen as control fungicide in the morphological study. **V-21** and TM were dissolved in DMF and Tween-80 at the concentration of 1000 mg L^{-1}. The culture media were obtained by mixing the solution of compound **V-21** in DMF with PDA, on which fungus cakes were placed. The blank test was made using DMF. The culture had been stored in an incubator at 24 ± 0.5 °C. When the diameter of mycelia in the blank control test grew to 2−3 cm, the culture media with mycelia were taken out for stained preparation. The morphology of the cell wall of *C. cassiicola* was observed using an optical microscope (*26*).

RESULTS AND DISCUSSION

Synthesis. The synthetic route of compounds **V** is shown in **Scheme 2**, where the starting materials were substituted anilines and benzoic acids. All of the target compounds were prepared by the nucleophilic addition reaction of 5-substituted-phenyl-2-furanmethanol with benzoyl isocyanate in the system without moisture. The reaction occurred in toluene at room temperature as soon as the benzoyl isocyanate was added into the solution containing 5-aryl-2-furanmethanol. The reaction should be kept at low temperature because the 5-aryl-2-furanmethanol easily decomposes when the temperature is > 80 °C.

All of the structures of title compounds were confirmed by ^{1}H NMR, IR, and elemental analyses. In the IR spectra, the compounds showed absorption bands around 3200 cm^{-1} originating from the N−H stretching vibration. The strong bands around 1750 cm^{-1} could be assigned to the C═O stretching vibration. The bands between 1690 and 1620 cm^{-1} were carbonyl vibration of the secondary amide. Absorption bands around 1510 and 1480 cm^{-1} were attributed to the frame vibration of the phenyl ring.

In the ^{1}H NMR spectrum, one sharp peak in the range from 11.36 to 11.71 ppm was due to the presence of NH. The splits of most compounds were normal except for the compounds with fluorine substitution because of the coupling and splitting between fluorine and hydrogen. The fluorine atom splits a hydrogen proton into a doublet, which complicated the proton signal. Mostly, the protons on phenyl rings were split into multiple peaks in the range from 7.10 to 7.90 ppm and the protons on the furan ring were split into a doublet in the range from 6.70 to 7.30 ppm. All of the CH_2 appeared in a single peak around 5.20 ppm.

Biological Activity. Considering that the lead compounds **B** and **C** had good insecticidal activities against dipterous and lepidopterous insects, we chose *C. pipiens pallens* and *P. xylostella* Linnaeus first to evaluate whether the designed compounds retained the insecticidal activity. Unfortunately, as shown in **Tables 3** and **4**, compounds **V** had no insecticidal effect on *C. pipiens pallens* even at 2000 mg L^{-1} or on *P. xylostella* Linnaeus at 600 mg L^{-1}. It is well-known that the BPUs were discovered dramatically when Wellinga from Philips-Duphar screened for herbicides in the 1970s (*5*). Our title compounds, in which the urea linkage was converted to carbamic acid ester by replacing NH with O, might have other activity instead of insecticidal activity.

Filippini (*27*) and Fukumoto (*28*) reported that compounds valiphenal and pyribencarb, which contain a carbamate moiety, showed excellent fungicidal activities and safety to crops and nontargeted organisms. Enlightened by the results from Filippini and Fukumoto, we turned to study fungicidal activities of the title

Table 2. ^{1}H NMR and IR Data of Compounds **V**

compd	^{1}H NMR (δ)	IR (ν, cm^{-1})
V-1	11.71 (s, 1H, NH), 7.81−7.75 (m, 1H, ArH-Fu), 7.60−7.54 (m, 1H, ArH), 7.39−7.29 (m, 3H, ArH-Fu), 7.20 (t, 2H, ArH), 6.86 (t, 1H, FuH), 6.76 (d, J = 3.36 Hz, 1H, FuH), 5.23 (s, 2H, CH_2)	3200, 1770, 1690, 1620, 1510, 1480, 1200
V-2	11.69 (s, 1H, NH), 7.60−7.45 (m, 4H, 3ArH-Fu + ArH), 7.22−7.13 (m, 3H, ArH-Fu + 2ArH), 7.08 (d, J = 3.39 Hz, 1H, FuH), 6.72 (d, J = 3.42, 1H, FuH), 5.21 (s, 2H, CH_2)	3200, 1780, 1690, 1610, 1520, 1480, 1200
V-3	11.70 (s, 1H, NH), 7.78−7.73 (m, 2H, ArH-Fu), 7.60−7.54 (m, 1H, ArH), 7.32−7.27 (m, 2H, ArH-Fu), 7.26−7.17 (m, 2H, ArH), 6.95 (d, J = 3.36 Hz, 1H, FuH), 6.70 (d, J = 3.39 Hz, 1H, FuH), 5.20 (s, 2H, CH_2)	3100, 1750, 1710, 1620, 1490, 1480, 1380, 1290
V-4	11.70 (s, 1H, NH), 7.85−7.77 (m, 1H, ArH-Fu), 7.60−7.54 (m, 1H, ArH), 7.47−7.40 (m, 1H, ArH-Fu), 7.27−7.16 (m, 3H, ArH-Fu + 2ArH), 6.83 (t, 1H, FuH), 6.75 (d, J = 3.39 Hz, 1H, FuH), 5.22 (s, 2H, CH_2)	3100, 1790, 1690, 1620, 1490, 1480, 1190
V-5	11.67 (s, 1H, NH), 7.81 (m, 1H, ArH-Fu), 7.59−7.44 (m, 3H, 2ArH-Fu + ArH), 7.40−7.37 (m, 1H, ArH-Fu), 7.22−7.17 (m, 2H, ArH), 7.12 (d, J = 3.45 Hz, 1H, FuH), 6.76 (d, J = 3.42, 1H, FuH), 5.23 (s, 2H, CH_2)	3200, 1770, 1700, 1630, 1530, 1490, 1220
V-6	11.68 (s, 1H, NH), 7.77−7.45 (m, 4H, 3ArH-Fu + ArH), 7.40−7.36 (m, 1H, ArH-Fu), 7.22−7.17 (m, 2H, ArH), 7.11 (d, J = 3.39, 1H, FuH), 6.72 (d, J = 3.42, 1H, FuH), 5.20 (s, 2H, CH_2)	3200, 1770, 1690, 1630, 1530, 1490, 1210
V-7	11.66 (s, 1H, NH), 7.75−7.70 (m, 2H, ArH-Fu), 7.62−7.49 (m, 3H, 2ArH-Fu + ArH), 7.24−7.16 (m, 2H, ArH), 7.02 (d, J = 3.36 Hz, 1H, FuH), 6.71 (d, J = 3.36 Hz, 1H, FuH), 5.20 (s, 2H, CH_2)	3200, 1770, 1690, 1630, 1490, 1480, 1200
V-8	11.69 (s, 1H, NH), 7.77−7.74 (m, 2H, ArH-Fu), 7.60−7.48 (m, 2H, ArH-Fu + ArH), 7.33−7.27 (m, 1H, ArH-Fu), 7.22−7.17 (m, 2H, ArH), 7.13 (d, J = 3.42 Hz, 1H, FuH), 6.76 (d, J = 3.45 Hz, 1H, FuH), 5.22 (s, 2H, CH_2)	3300, 1770, 1690, 1630, 1530, 1480, 1210
V-9	11.68 (s, 1H, NH), 7.68−7.52 (m, 5H, 4ArH-Fu + ArH), 7.23−7.16 (m, 2H, ArH), 7.03 (d, J = 3.39 Hz, 1H, FuH), 6.71 (d, J = 3.39 Hz, 1H, FuH), 5.20 (s, 2H, CH_2)	3200, 1770, 1680, 1630, 1480, 1350, 1190
V-10	11.71 (s, 1H, NH), 7.78−7.77 (m, 1H, ArH-Fu), 7.54−7.30 (m, 6H, 3ArH-Fu + 3ArH), 6.87−6.84 (m, 1H, FuH), 6.74 (br s, 1H, FuH), 5.21 (s, 2H, CH_2)	3200, 1770, 1690, 1490, 1440, 1340, 1190
V-11	11.71 (s, 1H, NH), 7.56−7.42 (m, 6H, 3ArH-Fu + 3ArH), 7.19−7.12 (m, 1H, ArH-Fu), 7.07 (d, J = 3.36 Hz, 1H, FuH), 6.71 (br s, 1H, FuH), 5.18 (s, 2H, CH_2)	3200, 1780, 1690, 1490, 1430, 1350, 1200
V-12	11.70 (s, 1H, NH), 7.77−7.71 (m, 2H, ArH-Fu), 7.54−7.42 (m, 3H, ArH), 7.33−7.25 (m, 2H, ArH-Fu), 6.94 (d, J = 3.33 Hz, 1H, FuH), 6.68 (br s, 1H, FuH), 5.17 (s, 2H, CH_2)	3200, 1780, 1690, 1490, 1430, 1350, 1190
V-13	11.70 (s, 1H, NH), 7.84−7.76 (m, 1H, ArH-Fu), 7.54−7.39 (m, 4H, ArH-Fu + 3ArH), 7.26−7.20 (m, 1H, FuH), 6.83−6.81 (m, 1H, FuH), 5.21 (s, 2H, CH_2)	3300, 1780, 1690, 1490, 1480, 1340, 1190
V-14	11.70 (s, 1H, NH), 7.82−7.78 (m, 1H, ArH-Fu), 7.59−7.34 (m, 6H, 3ArH-Fu + 3ArH), 7.11 (d, J = 3.42 Hz, 1H, FuH), 6.74−6.73 (m, 1H, FuH), 5.20 (s, 2H, CH_2)	3200, 1770, 1690, 1480, 1440, 1330, 1190
V-15	11.71 (s, 1H, NH), 7.76−7.75 (m, 1H, ArH-Fu), 7.68−7.65 (m, 1H, ArH-Fu), 7.54−7.42 (m, 4H, ArH-Fu + 3ArH), 7.40−7.36 (m, 1H, ArH-Fu), 7.10 (d, 1H, J = 3.36 Hz, FuH), 6.71−6.70 (m, 1H, FuH), 5.19 (s, 2H, CH_2)	3200, 1780, 1690, 1480, 1430, 1320, 1190
V-16	11.69 (s, 1H, NH), 7.74−7.70 (m, 2H, ArH-Fu), 7.54−7.42 (m, 5H, 2ArH-Fu + 3ArH), 7.01 (d, J = 3.36 Hz, 1H, FuH), 6.70−6.69 (m, 1H, FuH), 5.18 (s, 2H, CH_2)	3200, 1770, 1680, 1480, 1440, 1340, 1190
V-17	11.70 (s, 1H, NH), 7.72−7.71 (m, 2H, ArH-Fu), 7.53−7.44 (m, 4H, 2ArH-Fu + 2ArH), 7.33−7.27 (m, 1H, ArH), 7.12 (d, J = 3.42 Hz, 1H, FuH), 6.74−6.73 (m, 1H, FuH), 5.19 (s, 2H, CH_2)	3200, 1780, 1690, 1490, 1440, 1330, 1200
V-18	11.70 (s, 1H, NH), 7.68−7.61 (m, 4H, ArH-Fu), 7.54−7.40 (m, 3H, ArH), 7.02 (d, J = 3.36 Hz, 1H, FuH), 6.70 (br s, 1H, FuH), 5.17 (s, 2H, CH_2)	3200, 1770, 1690, 1490, 1440, 1350, 1190
V-19	11.38 (s, 1H, NH), 7.78−7.77 (m, 1H, ArH-Fu), 7.50−7.31 (m, 7H, 3ArH-Fu + 4ArH), 6.87−6.84 (m, 1H, FuH), 6.74 (d, J = 3.36 Hz, 1H, FuH), 5.20 (s, 2H, CH_2)	3200, 1780, 1680, 1500, 1430, 1220, 1040
V-20	11.37 (s, 1H, NH), 7.56−7.38 (m, 7H, 3ArH-Fu + 4ArH), 7.16−7.15 (m, 1H, ArH-Fu), 7.08 (d, J = 3.39 Hz, 1H, FuH), 6.70 (d, J = 3.42, 1H, FuH), 5.18 (s, 2H, CH_2)	3200, 1780, 1680, 1510, 1450, 1220, 1040
V-21	11.36 (s, 1H, NH), 7.77−7.72 (m, 2H, ArH-Fu), 7.50−7.38 (m, 4H, ArH), 7.32−7.26 (m, 2H, ArH-Fu), 6.94 (d, J = 3.33, 1H, FuH), 6.68 (d, J = 3.36 Hz, 1H, FuH), 5.17 (s, 2H, CH_2)	3150, 1780, 1680, 1490, 1430, 1220, 1040
V-22	11.36 (s, 1H, NH), 7.83−7.79 (m, 1H, ArH-Fu), 7.58−7.56 (m, 1H, ArH-Fu), 7.50−7.36 (m, 6H, 2ArH-Fu + 4ArH), 7.11 (d, J = 3.45 Hz, 1H, FuH), 6.74 (d, J = 3.45 Hz, 1H, FuH), 5.20 (s, 2H, CH_2)	3200, 1780, 1680, 1500, 1480, 1200
V-23	11.38 (s, 1H, NH), 7.76−7.75 (m, 1H, ArH-Fu), 7.69−7.65 (m, 1H, ArH-Fu), 7.50−7.36 (m, 6H, 2ArH-Fu + 4ArH), 7.10 (d, J = 3.36, 1H, FuH), 6.71 (d, J = 3.42 Hz, 1H, FuH), 5.18 (s, 2H, CH_2)	3200, 1780, 1680, 1520, 1480, 1220
V-24	11.36 (s, 1H, NH), 7.74−7.70 (m, 2H, ArH-Fu), 7.53−7.36 (m, 6H, 2ArH-Fu + 4ArH), 7.02 (d, J = 3.39 Hz, 1H, FuH), 6.69 (d, J = 3.39 Hz, 1H, FuH), 5.17 (s, 2H, CH_2)	3200, 1780, 1690, 1510, 1480, 1220
V-25	11.37 (s, 1H, NH), 7.77−7.73 (m, 2H, ArH-Fu + ArH), 7.53−7.39 (m, 5H, 2ArH-Fu + 3ArH), 7.32−7.29 (m, 1H, ArH), 7.12 (d, J = 3.45 Hz, 1H, FuH), 6.74 (d, J = 3.45 Hz, 1H, FuH), 5.19 (s, 2H, CH_2)	3200, 1770, 1690, 1500, 1470, 1200
V-26	11.37 (s, 1H, NH), 7.68−7.61 (m, 4H, ArH-Fu), 7.50−7.36 (m, 4H, ArH), 7.03 (d, J = 3.39 Hz, 1H, FuH), 6.69 (d, J = 3.39 Hz, 1H, FuH), 5.17 (s, 2H, CH_2)	3200, 1770, 1690, 1510, 1480, 1220, 1040

Scheme 2. General Synthetic Procedure for Target Compounds **V**

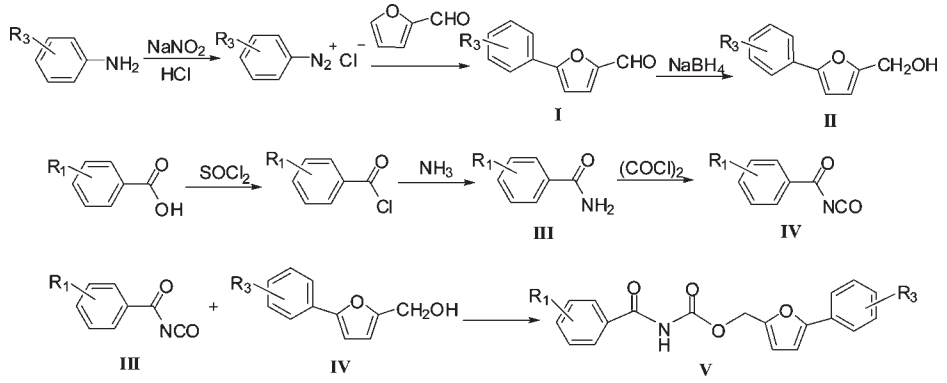


Table 3. Larvicidal Activity against *Culex pipiens pallens* at 2000 mg L^{-1}

compd	mortality (%)	compd	mortality (%)	compd	mortality (%)
V-1	0	**V-11**	10	**V-21**	10
V-2	10	**V-12**	0	**V-22**	20
V-3	0	**V-13**	10	**V-23**	0
V-4	10	**V-14**	0	**V-24**	10
V-5	0	**V-15**	10	**V-25**	0
V-6	10	**V-16**	0	**V-26**	10
V-7	10	**V-17**	0	**RH-5849**	100
V-8	20	**V-18**	10		
V-9	0	**V-19**	10		
V-10	0	**V-20**	10		

Table 4. Insecticidal Activity against *Plutella xylostella* Linnaeus at 600 mg L^{-1}

compd	mortality (%)	compd	mortality (%)	comp.	mortality (%)
V-1	0	**V-11**	20	**V-21**	0
V-2	0	**V-12**	0	**V-22**	0
V-3	10	**V-13**	1	**V-23**	0
V-4	0	**V-14**	0	**V-24**	0
V-5	0	**V-15**	10	**V-25**	0
V-6	0	**V-16**	10	**V-26**	0
V-7	0	**V-17**	0	CK	0
V-8	10	**V-18**	0	fipronil[a]	100
V-9	10	**V-19**	0		
V-10	10	**V-20**	0		

[a] The control fipronil was at 5 mg L^{-1}.

compounds, in which the urea linkage was converted to a carbamic acid ester. Four kinds of common plant pathogens, *C. cassiicola*, *T. cucumeris*, *B. cinerea*, and *F. oxysporum*, were chosen for bioassay. As shown in **Table 5**, most compounds showed good fungicidal activities in vitro against the above four strains at 50 mg L^{-1}. In general, compounds **V-1**−**V-9**, in which R_1 is a 2,6-F_2-substituted group, showed higher activities and broader spectra than compounds in which R_1 is a 2,6-Cl_2- or 2-Cl-substituted group. Compounds **V-4**, **V-6**, **V-7**, and **V-8** displayed higher activities against the four fungus species than those of the four control fungicides. Particularly, compound **V-7** showed excellent activities with inhibitory rates of 71.56, 95.31, 100.0, and 92.26%, respectively, whereas the four commercialized fungicides, 75% chlorothalonil WP, 3% jingangmycin AS, 40% pyrimethanil SC, and 70% thiophanate-methyl WP, displayed 23.29, 57.51, 48.90, and 34.21% inhibitory rates correspondingly. For the title compounds, their fungicidal activities against *T. cucumeris* were generally better than those against *F. oxysporum*.

As chitin is a major component of fungal cell walls, we chose compound **V-21** with a medium inhibitory rate to test if it would have an effect on the cell wall so as to identify whether the

Table 5. Fungicidal Activities of Compounds **V** against Four Fungus Species at 50 mg L^{-1}

	inhibitory rate(%)			
compd	*Corynespora cassiicola*	*Thanatephorus cucumeris*	*Botrytis cinerea*	*Fusarium oxysporum*
V-1	44.52 ± 4.04	46.22 ± 4.08	70.36 ± 2.16	44.58 ± 3.17
V-2	31.51 ± 2.22	38.35 ± 2.29	60.36 ± 2.06	7.63 ± 0.79
V-3	22.07 ± 1.11	56.05 ± 3.33	58.47 ± 3.25	49.43 ± 2.55
V-4	42.45 ± 3.28	61.28 ± 5.45	64.00 ± 4.04	44.58 ± 3.31
V-5	43.49 ± 4.15	36.59 ± 2.26	66.62 ± 3.18	41.22 ± 2.29
V-6	50.52 ± 4.64	64.88 ± 3.19	63.55 ± 2.78	45.40 ± 6.05
V-7	71.56 ± 5.15	95.31 ± 8.08	100.00 ± 0.00	92.26 ± 7.78
V-8	52.16 ± 3.25	60.59 ± 4.06	54.31 ± 3.15	42.33 ± 3.23
V-9	57.75 ± 4.41	63.33 ± 7.05	62.24 ± 2.25	7.38 ± 1.05
V-10	36.00 ± 1.25	70.36 ± 6.52	57.28 ± 5.01	1.50 ± 0.13
V-11	12.89 ± 0.75	61.97 ± 5.85	32.56 ± 2.07	8.82 ± 0.99
V-12	37.33 ± 1.32	72.73 ± 9.05	37.07 ± 3.31	35.28 ± 2.02
V-13	15.97 ± 0.98	63.33 ± 6.79	27.89 ± 5.08	15.86 ± 1.12
V-14	34.66 ± 2.22	83.10 ± 10.07	41.42 ± 2.15	35.28 ± 1.11
V-15	19.00 ± 1.04	53.31 ± 3.25	12.96 ± 2.22	14.47 ± 1.07
V-16	33.31 ± 2.11	67.89 ± 6.18	48.06 ± 3.16	44.59 ± 3.12
V-17	39.94 ± 2.36	79.25 ± 7.08	44.79 ± 3.17	42.33 ± 2.24
V-18	54.44 ± 1.28	64.66 ± 4.86	52.78 ± 3.19	32.83 ± 1.18
V-19	26.33 ± 0.79	65.32 ± 5.05	34.38 ± 2.78	1.50 ± 0.23
V-20	37.33 ± 3.14	53.31 ± 2.26	48.87 ± 3.45	14.47 ± 0.75
V-21	38.64 ± 2.38	60.59 ± 3.34	40.56 ± 4.06	4.46 ± 0.27
V-22	43.75 ± 4.03	69.75 ± 5.25	25.02 ± 2.12	0.00 ± 0.00
V-23	24.89 ± 1.85	38.64 ± 3.16	24.05 ± 1.78	−3.03 ± 0.05
V-24	65.97 ± 5.06	75.55 ± 7.05	55.06 ± 3.37	14.47 ± 1.11
V-25	42.49 ± 2.25	67.26 ± 6.17	54.31 ± 3.64	25.24 ± 2.18
V-26	59.89 ± 3.33	50.22 ± 2.26	34.38 ± 3.29	10.25 ± 0.68
DMF (control)	1.66 ± 0.75	0.00 ± 0.00	1.11 ± 0.15	11.67 ± 0.88
fungicides[a]	23.29 ± 1.25 a	57.51 ± 3.35 b	48.90 ± 2.77 c	34.21 ± 2.28 d

[a] Control fungicides: a, 75% chlorothalonil WP; b, 3% jingangmycin AS; c, 40% Pyrimethanil SC; d, 70% thiophanate-methyl WP.

formation of chitin had been disrupted or not. The morphologic results are shown in **Figure 1**. Compared with the blank and fungicide control, the cytoplasm color of *C. cassiicola* treated with **V-21** turned purple, the same color as with the control fungicide TM. This phenomenon implied that **V-21** probably had the same effect on the cell wall of *C. cassiicola* as the fungicide control. In other words, **V-21** might disturb the formation of chitin in the cell wall.

In summary, a novel series of aryl carbamic acid 2-furanmethyl esters were designed and synthesized on the basis of the lead compounds **B** and **C**. Compared with the lead compounds, the title compounds showed no insecticidal activity against *C. pipiens pallens* and *P. xylostella* Linnaeus, but, inspiringly, they possessed obvious fungicidal activities against four kinds of common plant

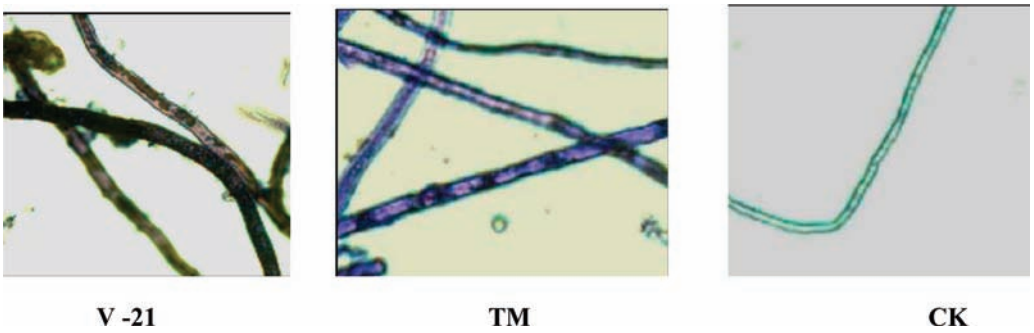


Figure 1. Morphology observation of cell wall of *Corynespora cassiicola* disposed by **V-21**, 5-thiophanate methyl (TM), and CK (DMF).

pathogens. In particular, compounds **V-4**, **V-6**, **V-7**, and **V-8** displayed higher activities against the four fungus species than those of the four control fungicides. Furthermore, the morphologic results suggested that compound **V-21** had an effect on the cell wall of *C. cassiicola*. The results indicated that the modification on the urea linkage of lead compounds was an effective strategy to discover new candidates as fungicides.

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