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Synthesis and Antifungal Activity of β-Trifluoroalkyl Aminovinyl Ketone Derivatives

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Ten β-trifluoroalkyl aminovinyl ketone derivatives were synthesized, and their inhibitory effects on several phytopathogenic fungi, an oomycete and plants were assessed. The various compounds were fungitoxic at the 10−100 μM range, with (*Z*)-3-amino-4,4,4-trifluoro-1-(4-chlorophenyl)but-2-en-1-one exhibiting the highest inhibitory effect on most of the test pathogens. *Alternaria alternata* and *Neurospora crassa* were the most tolerant and sensitive fungi to the compounds, respectively. We propose that (*Z*)-3-amino-4,4,4-trifluoro-1-phenylbut-2-en-1-one is the minimal structural requirement for a β-trifluoroalkyl aminovinyl ketone fungitoxic derivative.

KEYWORDS: Antifungal; β-trifluoroalkyl aminovinyl ketone derivatives; structure−activity relationship; *Alternaria alternata*; *Penicillium digitatum*; *Rhizoctonia soliani*; *Botrytis cinerea*; *Sclerotinia sclerotiorum*; *Neurospora crassa*; *Pythium aphanidermatum*

INTRODUCTION

In many agricultural practices, fungicides are extensively used to prevent and curb the progression of plant diseases that have severe adverse effects on crop yields and quality. In some cases, the prolonged and repeated use of many fungicides has resulted in the proliferation of plant pathogen isolates that are resistant to the fungicides employed. Therefore, identifying new classes of antifungal compounds based on structures not previously used in combating plant diseases may assist in the control of plant pathogens that are tolerant or resistant to known compounds.

Sclerotinia sclerotiorum and *Botrytis cinerea* are necrotrophic phytopathogenic filamentous ascomycetes known to attack more than 400 and 200 plant species, respectively (*1*−*7*). Diseases caused in economically important plants by these fungi occur worldwide, cause considerable damage, and have proven difficult to control (culturally or chemically), and host resistance to these fungi is inadequate. Annual losses of crops from diseases caused by *S. sclerotiorum* and *B. cinerea* are in the multimillion dollar range (e.g., http://www.whitemoldresearch.com). In addition, their ubiquitous prevalence along with the intensive use of fungicides for their control has resulted in repeated appearance of fungicide-resistant strains (*8*−*11*). In order to expand the range of chemicals that could potentially be harnessed to control these fungi, we have synthesized a group of (*Z*)-β-trifluoroalkyl aminovinyl ketones and assessed their fungitoxic activity. We have determined that some of these compounds can curb fungal growth at the 10−100 μM range. The potential utilization of these molecules is supported by the fact that synthesis of these compounds consists of two simple stages using inexpensive and commercially available compounds.

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MATERIALS AND METHODS

Analytical HPLC was performed on a 250 × 4.2 mm Lichroprep RP-18 column from Merck, with a 1 mL/min flow and detection at 214 nm. The eluents were triply distilled water and HPLC-grade CH_3CN (containing 0.1% TFA) or MeOH. Mass spectra were measured in the positive and negative modes using a quadrupole mass spectrometer equipped with an electrospray ionization source and cross-flow inlet. ^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively in $CDCl_3$, unless otherwise indicated. Assignments in the final products were supported by 2D COSY, HMBC and HMQC spectroscopy. All chemical shifts are reported with respect to TMS. Chromatography was carried out by standard flash chromatography and TLC on silica gel (Merck 7735).

Compounds and Syntheses. *Preparation of Trifluoroacetonitrile*. Sulfuric acid (2 mL) was slowly added to 100 mL of methanol while stirring in an ice bath. Trifluoroacetic acid (118 gr, 78 mL) was added to the cooling methanol solution. The mixture was stirred while heating (40−45 °C) for 6 h. After cooling to rt, water was added and the resulting trifluoromethyl ester organic phase was separated and dried over anhydrous sodium sulfate. After filtration, 1 L of a 2.0 M solution of ammonia in methanol was added to the filtrate, and the mixture was stirred overnight. Solvent and unreacted ammonia were evaporated, and the white solid was dried under vacuum (98 g) and used for the next step without any further purification. The obtained trifluoroacetamide was rapidly mixed with phosphorus pentaoxide (P_2O_5) (in 3-fold excess) in a 500 mL flask (the condensation reaction starts immediately). The reaction mixture was heated to 150 °C, and the obtained gaseous trifluoroacetonitrile was directly bubbled into the following reaction.

General Procedure for Preparation of β-Trifluoroalkyl Aminovinyl Ketones ***5a*****−*****j***. 4 mmol of acetophenone was added in a dropwise manner to a mixture of 10 mmol of sodium *tert*-butoxide in

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100 mL of dry THF. Then, trifluoroacetonitrile (produced from 15 g of amide and 45 g of P_2O_5) was bubbled in for 2 h to the reaction vessel equipped with a dry ice−acetone condenser. After bubbling, the mixture was stirred for 5 h at rt. A solution (10 mmol) of commercial HCl−dioxane 4 N was added dropwise, and after 10 min the mixture was filtrated and dioxane was evaporated under vacuum. The crude product was recrystallized from hexane.

Preparation of (*Z*)*-4-(3-Amino-4,4,4-trifluorobut-2-enoyl)benzonitrile* (***5a***). Compound **5a** was prepared from **3** and 4-cyanoacetophenone (1 g, 6.9 mmol) following the general procedure described above. Purification by column chromatography on silica gel using *n*-hexane−EtOAc (8:2) as eluent, yielded 1.44 g of **5a** (87% yield) as a colorless oil: ν_{max} (KBr) 2880, 1670, 1635, 1270 cm^{-1}; HRMS (DI, *m*/*z*) calcd for $C_{11}H_7F_3N_2O$ (MH^+) 241.05, found 241.04; ^1H NMR ($CDCl_3$) δ 6.19 (s, 1, CH═C), 7.68 (d, 2, *J* = 10.7 Hz, H-2), 8.14 (d, 2, *J* = 10.7 Hz, H-3); ^{13}C NMR (δ, ppm, $CDCl_3$) 189.7, 160.7, 142.2, 132.7, 131.5, 130.6, 118.4, 115.7, 95.5.

Preparation of (*Z*)*-3-Amino-4,4,4-trifluoro-1-(4-fluorophenyl)but-2-en-1-one* (***5b***). Compound **5b** was prepared from **3** and 4-fluoroacetophenone (1 g, 7.3 mmol) following the general procedure described above. Purification by column chromatography on silica gel using *n*-hexane−EtOAc (8:2) as eluent yielded 1.28 g of **5b** (85% yield) as a colorless oil: ν_{max} (KBr) 1670, 1650, 1190 cm^{-1}; HRMS (DI, *m*/*z*) calcd for $C_{10}H_7F_4NO$ (MH^+) 234.046, found 234.052; ^1H NMR ($CDCl_3$) δ 6.19 (s, 1, CH═C), 7.06 (t, 2, *J* = 5.35 Hz, H-3), 7.66 (m, 2, H-2); ^{13}C NMR (δ, ppm, $CDCl_3$) 189.7, 168.7, 160.7, 133.5, 131.5, 116, 95.5.

Preparation of (*Z*)*-3-Amino-4,4,4-trifluoro-1-(4-chlorophenyl)but-2-en-1-one* (*5c*). Compound **5c** was prepared from **3** and 4-chloroacetophenone (1 g, 6.5 mmol) following the general procedure described above. Purification by column chromatography on silica gel using *n*-hexane−EtOAc (8:2) as eluent yielded 1.38 of **5c** (81% yield) as a colorless oil: ν_{max} (KBr) 1670, 1590, 1380, 1060 cm^{-1}; HRMS (DI, *m*/*z*) calcd for $C_{10}H_7ClF_3NO$ (MH^+) 250.017, found 250.020: 252.018 (3:1); ^1H NMR ($CDCl_3$) δ 6.19 (s, 1, CH═C), 7.41 (d, 2, *J* = 10.7 Hz, H-3), 7.82 (d, 2, *J* = 10.7 Hz, H2). ^{13}C NMR (δ, ppm, $CDCl_3$) 189.7, 160.7, 140.1, 136, 131.5, 131.3, 129.3, 95.0.

Preparation of (*Z*)*-3-Amino-4,4,4-trifluoro-1-(4-hydroxyphenyl)but-2-en-1-one* (***5d***). Compound **5d** was prepared from **3** and 4-hydroxyacetophenone (1 g, 7.4 mmol) following the general procedure described above. Purification by column chromatography on silica gel using *n*-hexane−EtOAc (6:4) as eluent yielded 1.19 g of **5d** (76% yield) as a white powder; ν_{max} (KBr) 3500−3180 (bs), 1660, 1520, 1450, 1230 cm^{-1}; HRMS (DI, *m*/*z*) calcd for $C_{10}H_8F_3NO_2$ (MH^+) 232.05, found 232.04; ^1H NMR ($CDCl_3$) δ 6.19 (s, 1, CH═C), 6.89 (d, 2, *J* = 10.7 Hz, H-3), 7.82 (d, 2, *J* = 10.7 Hz, H-2); ^{13}C NMR (δ, ppm, $CDCl_3$) 189.7, 164.3, 160.7, 131.3, 130.5, 125.5, 116.4, 94.5.

Preparation of (*Z*)*-tert-Butyl-4-(3-amino-4,4,4-trifluorobut-2-enoyl)phenyl carbamate* (***5e***). Compound **5e** was prepared from **3** and 4-BOC-amino acetophenone (1 g, 4.3 mmol) following the general procedure described above. Purification by column chromatography on silica gel using *n*-hexane−EtOAc (6:4) as eluent yielded 1.01 g of **5e** (72% yield) as a colorless oil: ν_{max} (KBr) 1660, 1500, 1350, 1120 cm^{-1}; HRMS (DI, *m*/*z*) calcd for $C_{15}H_{17}F_3N_2O_3$ (MH^+) 331.119, found 331.126; ^1H NMR ($CDCl_3$) δ 1.5 (s, 9, ^{t}Bu), 6.19 (s, 1, CH═C), 7.45 (d, 2, *J* = 10.7 Hz, H-3), 7.85 (d, 2, *J* = 10.7 Hz, H-2); ^{13}C NMR (δ, ppm, $CDCl_3$) 189.7, 164.3, 160.7, 131.5, 131.3, 130.5, 116.4, 90.0.

Preparation of (*Z*)*-3-Amino-4,4,4-trifluoro-1-(naphthalen-2-yl)but-2-en-1-one* (***5f***). Compound **5f** was prepared from **3** and acetonaphthone (1 g, 5.9 mmol) following the general procedure described above. Purification by column chromatography on silica gel using *n*-hexane−EtOAc (7:3) as eluent yielded 1.11 g of **5f** (74% yield) as a colorless oil: ν_{max} (KBr) 1655, 1570, 1360, 1240 cm^{-1}; HRMS (DI, *m*/*z*) calcd for $C_{14}H_{10}F_3NO$ (MH^+) 266.071, found 266.077; ^1H NMR ($CDCl_3$) δ 6.19 (s, 1, CH═C), 7.58 (m, 3, H-3,7,8), 7.99 (m, 3, H-4,5,6), 8.40 (s, 1, H-2); ^{13}C NMR (δ, ppm, $CDCl_3$) 189.7, 160.7, 135.6, 134.7, 132.5, 131.5, 129.5, 128.6, 128.5, 128.3, 127.7, 126.9, 124.2, 93.0.

Preparation of (*Z*)*-3-Amino-4,4,4-trifluoro-1-(3-(trifluoromethyl)phenyl)but-2-en-1-one* (***5g***). Compound **5g** was prepared from **3** and 3-trifluoromethyl acetonaphthone (1 g, 4.29 mmol) following the general procedure described above. Purification by column chromatography on silica gel using *n*-hexane−EtOAc (8:2) as eluent yielded 1.02 of **5g** (84% yield) as a colorless oil: ν_{max} (KBr) 1665, 1570, 1360, 1240 cm^{-1}; HRMS (DI, *m*/*z*) calcd for $C_{11}H_7F_6NO$ (MH^+) 284.048, found 284.051; ^1H NMR ($CDCl_3$) δ 6.21 (s, 1, CH═C), 7.6 (t, 1, *J* = 8.82 Hz, H-3), 7.8 (d, 2, *J* = 8.82 Hz, H-2), 8.09 (d, 2, *J* = 8.82 Hz, H-4), 8.19 (s, 1, H-6); ^{13}C NMR (δ, ppm, $CDCl_3$) 189.7, 160.7, 138.2, 133.2, 131.5, 130.9, 129.6, 126.2, 124.2, 94.0.

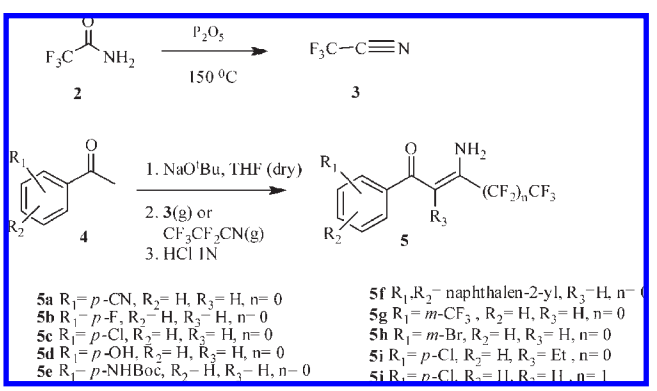
Preparation of (*Z*)*-3-Amino-1-(3-bromophenyl)-4,4,4-trifluorobut-2-en-1-one* (***5h***). Compound **5h** was prepared from **3** and 3-bromoacetophenone (1 g, 5.0 mmol) following the general procedure described above. Purification by column chromatography on silica gel using *n*-hexane−EtOAc (8:2) as eluent yielded 1.32 g of **5h** (89% yield) as a colorless oil: ν_{max} (KBr) 1675, 1640, 1410. 1305, 1060 cm^{-1}; HRMS (DI, *m*/*z*) calcd for $C_{10}H_7BrF_3NO$ (MH^+) 294.295, found 293.972, 295.974 (1:1); ^1H NMR ($CDCl_3$) δ 6.19 (s, 1, CH═C), 7.38 (t, 1, *J* = 6.25, 1H, H-4), 7.69 (d, 1 *J* = 12.5 Hz, H-3), 7.81 (d, 1, *J* = 12.5 Hz, H-2), 8.09 (s, 1, H-6). ^{13}C NMR (δ, ppm, $CDCl_3$) 189.7, 160.7, 140.1, 137.4, 133.4, 131.5, 128.9, 123.6, 95.5.

Preparation of (*Z*)*-3-Amino-1-(4-chlorophenyl)-2-ethyl-4,4,4-trifluorobut-2-en-1-one* (***5i***). Compound **5i** was prepared from **3** and 4-chlorobutyrophenone (1 g, 5.5 mmol) following the general procedure described above. Purification by column chromatography on silica gel using *n*-hexane−EtOAc (8:2) as eluent yielded 1.17 g of **5i** (68% yield) as a colorless oil: ν_{max} (KBr) 1665, 1630, 1390 cm^{-1}; HRMS (DI, *m*/*z*) calcd for $C_{12}H_{11}ClF_3NO$ (MH^+) 277.048, found 277.043:277.044 (3:1); ^1H NMR ($CDCl_3$) δ 0.98 (t, 3, *J* = 9.31 Hz, CH_2CH_3), 2.00 (q, 2, *J* = 9.31 Hz, C═CCH_2CH_3), 7.51 (d, 2, *J* = 10.34, H-3), 7.86 (d, 2, *J* = 10.34, H-4); ^{13}C NMR (δ, ppm, $CDCl_3$) 190.5, 152.5, 140.1, 136, 131.3, 129.3, 125.3, 112.9, 12.6, 11.6.

Preparation of (*Z*)*-3-Amino-1-(4-chlorophenyl)-4,4,5,5,5-pentafluoropent-2-en-1-one* (***5j***). Compound **5j** was prepared from gaseous 2,2,3,3,3-pentafluoropropanenitrile (prepared from commercial $CF_3CF_2CONH_2$ in the same manner as for **3** and 4-chlorobutyrophenone (1 g, 6.9 mmol) following the general procedure. Purification by column chromatography on silica gel using *n*-hexane−EtOAc (8:2) as eluent yielded 1.18 g of **5j** (57% yield) as a colorless oil: ν_{max} (KBr) 1660, 1600, 1470, 1290 cm^{-1}; HRMS (DI, *m*/*z*) calcd for $C_{11}H_{17}ClF_5NO$ (MH^+) 300.014, found 300.016:302.017 (3:1); ^1H NMR ($CDCl_3$) δ 6.23 (s, 1, CH═C), 7.40 (d, 2, *J* = 10.7 Hz, H-3), 7.84 (d, 2, *J* = 10.7 Hz, H-4; ^{13}C NMR (δ, ppm, $CDCl_3$) 191.2, 161.6, 141.7, 1364, 136.9, 133.8, 130.6, 127.1, 97.3.

Fungal Strains and Culturing Conditions. The fungi *Sclerotinia sclerotiorum* (isolate 1980 (*12*)), *Botrytis cinerea* (isolate BcI16 (*13*)), *Penicillium digitatum* (*14*), *Alternaria alternata* and *Rhizoctonia solani* (both from the fungal collection of the Dept. of Plant Pathology and Microbiology) and *Neurospora crassa* (strain *74-OR23-1*A, The Fungal Genetics Stock Center (*15*)) were used during this study. In addition, the oomycete *Pythium aphanidermatum* (from the Dept. of Plant Pathology and Microbiology) was also used as a test organism. Strains were cultured on potato dextrose agar (PDA, Difco Laboratories, Detroit, MI), unless otherwise stated.

Scheme 1. General Synthesis of ***β***-Trifluoroalkyl Aminovinyl Ketone Derivatives **5a**−**j**



Assessment of Fungitoxicity. Initial toxicity against the fungi (excluding *S. sclerotiorum*) and the oomycete was assessed by culturing the test organsims on Petri dishes containing 10 mL of PDA amended with either 10 or 100 μM of the ten original test compounds. Stock solutions of the different compounds were prepared in dimethyl sulfoxide (DMSO), and aliquots (not exceeding 0.001% v/v, a concentration that had no observable effect on the test organisms) were added to warm (50 °C) sterile medium prior to dispensing to the Petri dishes. *S. sclerotiorum* and *B. cinerea* were used for the advanced phase of tests, where the effects of compound concentrations (0−50 μM) were tested. The two fungi were cultured at 17 and 22 °C, respectively, for 48 h, after which radial growth was measured and compared to that of the fungal strains cultured in medium not amended with the antifungal compounds.

RESULTS AND DISCUSSION

Phenyl α,β-unsaturated carbonyl derivatives of cinnamic and coumaric are known backbones found in potent compounds in antifungal discovery (*16*). In recent years research based on these core structures has become an important tool for the generation of new leads and for providing access to diverse chemical entities with novel structures and properties (*17*). We decided to explore additional compounds that share some similarity with the cinnamic acid backbone in a scaffold hopping strategy toward the generation of novel antifungal compounds. In order to identify potential antifungal compounds, we designed and synthesized β-trifluoroalkyl aminovinyl ketone molecules that differed in the R_1, R_2, and R_3 substituents as well as in the length of the fluorocarbon chain in the scaffold (structure **5** in **Scheme 1**).

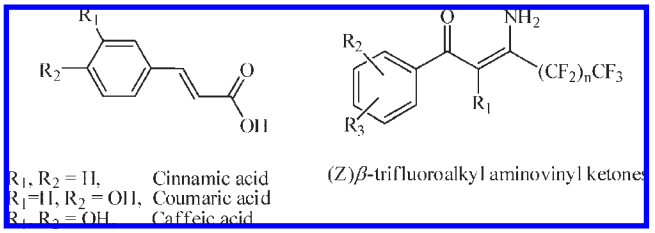


Figure 1. Structure of the compounds prepared in this study.

Several synthetic routes to the synthesis of fluoroalkyl-containing β-aminovinyl ketones starting from unsymmetrical fluoroalkyl-containing β-diketones and amines have been previously described (*18*−*21*). Unfortunately, these reactions result in poor to moderate yields. We adopted a different approach for trifluoroalkyl β-aminovinyl ketone synthesis: namely, condensation of trifluoroacetonitrile (*22*) with acetophenones in the presence of a strong base in dry aprotic solvents. After examining several alternatives, sodium *tert*-butoxide (NaO^{t}Bu) and dry THF were chosen as a base and solvent of choice respectively. This general method was applied very successfully in the preparation of **5a**−**j** (**Scheme 1**). Thus, we initially prepared gaseous $CNCF_3$ (**3**) from the corresponding trifluoroacetamide by dehydration with P_2O_5 at high temperature. Compound **3** was then directly bubbled into the reaction mixture of the appropriate acetophenone in the presence of NaO^{t}Bu under nitrogen atmosphere in dry THF. The reaction vessel was equipped with an acetone/dry ice cold-finger to avoid the undesired escape of gaseous **3**. After completion (monitored by TLC and HPLC), the reactions were quenched with dilute HCl, resulting in crude products that after

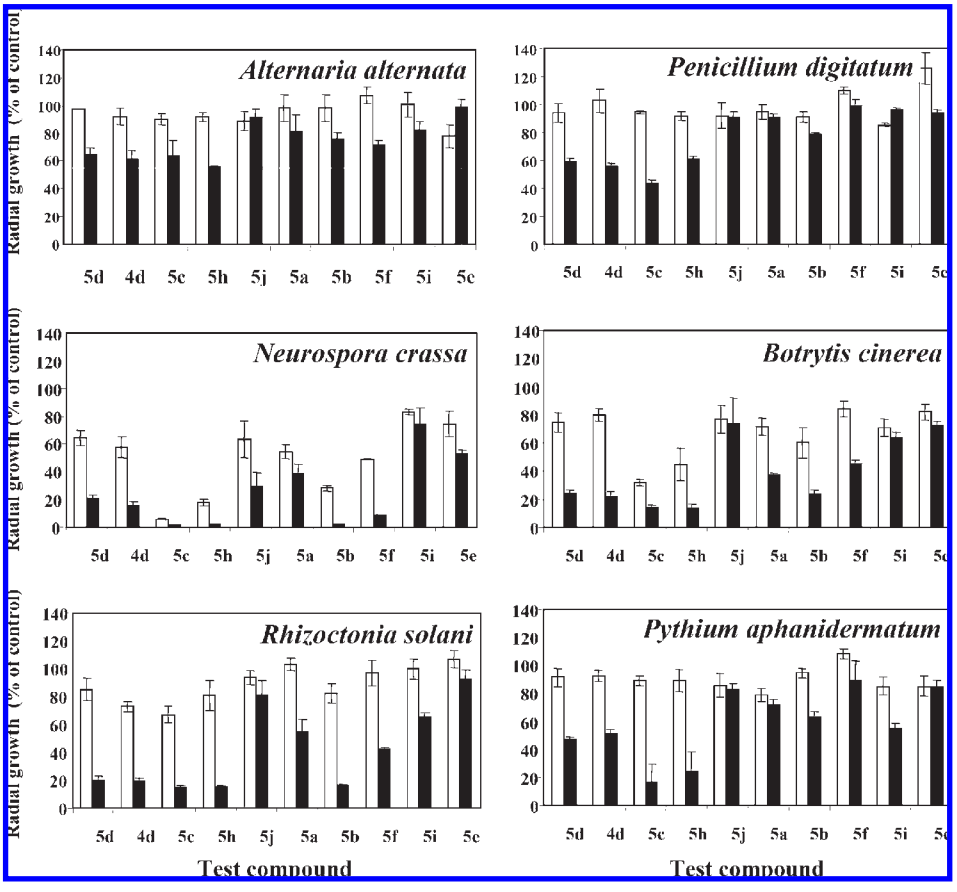


Figure 2. Effect of nine β-trifluoroalkyl aminovinyl ketone derivatives on radial growth of six test organisms. Test organisms were cultured on potato dextrose agar in the presence of either 10 or 100 μM concentrations (empty and full bars, respectively) of the various compounds. Y-error bars indicate standard deviation.

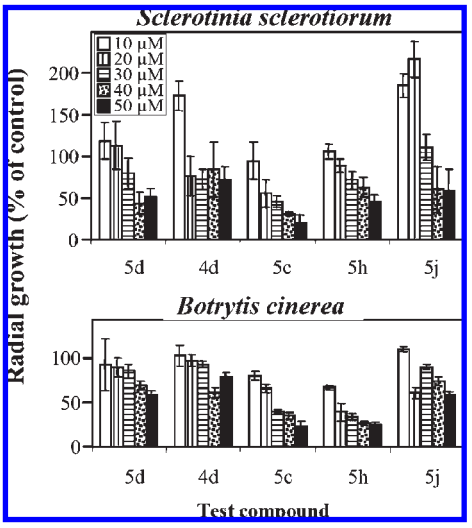


Figure 3. Effect of five β-trifluoroalkyl aminovinyl ketone derivatives on radial growth of *Sclerotina sclerotiorum* and *Botrytis cinerea*. Y-error bars indicate standard deviation.

subsequent purification by flash chromatography on silica gel (EtOAc/ *n*-hexane), pure **5a**−**i** were obtained in good yields (68−89%). Even a compound with the longer flourocarbone chain (**5j**) was prepared in the same manner as **5a**−**i**, using gaseous 2,2,3,3,3-pentafluoropropanenitrile (initially prepared from commercial $CF_3CF_2CONH_2$ and P_2O_5) and 4-chlorobutyrophenone in 57% yield .

Coumaric and cinnamic acids (**Figure 1**), but not caffeic acid, have been shown to be inhibitory to fungal (*Aspergillus* 'spp') growth (*23*). Apparently, the location of the substituent on the cinnamic acid backbone plays crucial role in determining the antifungal activity of the compound. This data prompted us to examine other phenyl α,β-unsaturated carbonyl scaffolds substituted with different functional groups at various locations and study their potential antifungal activity.

Almost all of the synthesized compounds exhibited some degree of toxicity toward the filamentous fungi tested (**Figure 2**). Nonetheless, significant differences in toxicity were observed among these compounds. For example, the highest toxicity levels were evident when with (*Z*)-3-amino-4,4,4-trifluoro-1-(4-chlorophenyl)but-2-en-1-one (**5c**) was present in the growth medium, while **5j**, **5i** and **5e**, respectively, were significantly less toxic. The fungi least susceptible to most of the compounds tested were *A. alternata* and *P. digitatum*. None of the compounds tested inhibited radial growth of *A. alternata* more than 50% (even at a 100 μM concentration) and only **5c** inhibited *P. digitatum* by more than 50%. In contrast, *N. crassa* appeared to be the most sensitive to the compounds at the higher concentrations tested, **5c**, **5h** and **5b** inhibited radial growth almost entirely. The oomycete *P. aphanidermatum* was sensitive to higher concentrations of **5d**, **4d**, **5c** and **5h**. The other compounds tested inhibited its radial growth only to a limited extent. Based on the outcome of the initial assessment of toxicity of the compounds to the test organisms, we decided to focus our analysis on five of the original compounds tested **5d**, **4b**, **5c**, **5h** and **5j** and their toxicity to the omnivorus phytopathogen *B. cinerea* and an additional broad-host pathogen related to *B. cinerea*: *S. sclerotiorum*. This analysis allowed us to determine if these phylogenetically related pathogens differ in their sensitivity to the structurally related tested compounds. In most instances, the fungal response to the tested compounds was dose dependent (**Figure 3**). Both fungi exhibited very similar sensitivity to **5d** and **5c**. Commercially available **4d**, that lacks the trifluoroprop-1-en-2-amine part in the backbone, was the least active compound and, interestingly, at the lower concentrations may have even stimulated the radial growth of *S. sclerotiorum*. This was also evident at the lower concentrations of **5j**. Overall, the most effective compound (in terms of curbing radial growth) was **5h**, even though the sensitivity of *B. cinerea* to this compound was significantly higher, at all concentrations, than that of *S. sclerotiorum*. Based on the results obtained it appears that (*Z*)-3-amino-4,4,4-trifluoro-1-phenylbut-2-en-1-one is the minimal scaffold for presenting β-trifluoroalkyl aminovinyl ketone fungitoxic activity, preferably substituted with a weak electron withdrawal halogen atom at *para* or *meta* positions. These findings emphasize the potential that some of these molecules have for fungicide development. Some of these compounds are potential leads to be considered for practical use, therefore, future full analysis of their biological activities need to be determined. One of these is their potential phytotoxicity. To that end, we performed preliminary tests on effect of the presence of the compounds on seed germination of alfalfa (*Medicago sativa* L.) and on induced phytotoxic response on leaves of tomato (Solanum lycopersicum L.), which are both hosts of *B. cinerea* and *S. sclerotiorum*. In all cases, no significant phytotoxic effects were observed (Gellerman et al., unpublished results). Work is in progress to assess the phytotoxic effects of this family of compounds.

Taken together, we have determined that a novel group of compounds, sharing the β-trifluoroalkyl aminovinyl ketone scaffold, exhibit antifungal activities *in vitro*. On the one hand, their activity is evident at relatively high concentrations (similar to those determined for most cinnamic acid derivatives described by Bisogno et al. (*16*)), even though at the highest tested concentrations fungal inhibition was not complete. On the other hand, the ease of synthesis of these stable compounds along with their apparent lack of phytotoxicity makes these compounds attractive for future consideration as potential components of antifungal intervention.

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Supporting Information Available: NMR spectra of compounds **5a**−**c**,**h** and HRMS of compounds **5c**,**f**−**h**. This material is available free of charge via the Internet at http://pubs.acs.org.

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