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ARTICLE

Design, Synthesis and Effect of the Introduction of a Propargyloxy Group on the Fungicidal Activities of 1-Substituted Phenoxypropan-2-Amino Valinamide Carbamate Derivatives

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Jian-Qiang Li, Zhi-Peng Wang, Yang Gao and Wei-Guang Zhao*

The cell walls of oomycetes are composed of cellulose, making cellulose synthase enzymes good targets for carboxylic acid amide fungicides. Valinamide carbamates are amino acid fungicides that represent excellent alternatives to conventional synthetic pesticides in terms of their ability to reduce the negative impacts of these compounds on human health and the environment. In a continuation of our research towards the development of new cellulose synthase inhibitors, we have developed a series of "stretched" analogues of iprovalicarb by the introduction of an additional OCH_2 linker. The bioassay results indicated that compounds containing a small group at the *para*-position of phenyl gave excellent fungicidal activities with EC_{50} values ranging from 0.59 to 2.06μmol L^{-1}. Most notably, the introduction of a propargyloxy group led to a pronounced increase in the fungicidal activity. Furthermore, compound **7o** bearing a propargyloxy group was identified as the most promising candidate because of its excellent fungicidal potency against oomycete diseases and good fungicidal activity against non-oomycete diseases.

Introduction

Oomycetes can lead to the occurrence of several destructive diseases in a range of important crop plants, such as late blight on potatoes, blue mold on tobacco, and grape downy mildew.[1] Fungicides are therefore vital for increasing the yield of food production processes. However, the overuse of traditional pesticides has led to several environmental issues during the last decade, which have raised public concerns regarding their use. The use of environmental friendly and biodegradable green pesticides could address some of these environmental problems, while maintaining crop yields. Amino acids are important biochemical molecules that are critical to life. The valinamide carbamates, which are amino acid fungicides, represent an excellent alternative to conventional synthetic pesticides in terms of their impact on human health and the environment. The valinamide carbamates, including benthiavalicarb,[2] iprovalicarb,[3] and valifenalate,[4] belong to one of three sub-classes of carboxylic acid amide (CAA) fungicides (FRAC code: 40),[5] which were officially announced by the Fungicide Resistance Action Committee (FRAC) in 2005.[1] In terms of their mode of action, these compounds target the cellulose synthase enzymes found in oomycete plant pathogens.[6, 7]

Mandipropamid,[8-10] which was developed by Syngenta, is the only mandelic acid amide fungicide to have been commercially marketed throughout the world to date. Lamberth et al.[10, 11] reported that mandelamide fungicides bearing an OCH_2 or CH_2OCH_2 linker between the 4-chlorophenyl ring and the 2-propargyloxyacetamide function of mandipropamid exhibited improved levels of fungicidal activity. For example, these "stretched" mandelamide systems showed improved activity against *P. infestans* with an increase in activity from 0.1 to 0.02 mg L^{-1} versus the parent system.

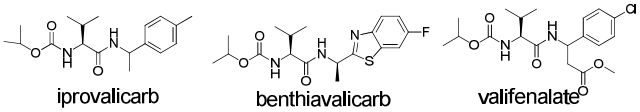

Fig. 1 Structures of commercial valinamide carbamates fungicides

In our previous study,[12-18] we reported the synthesis and evaluation of the fungicidal activities of a series of mandelic acid amide and valinamide carbamate derivatives. We also found that "stretched" valinamide carbamate derivatives bearing an OCH_2 linker between both of their phenyl rings exhibited much higher fungicidal activities against *Phytophthora capsici* and *Pseudoperonospora cubensis* than the corresponding lead compounds with two phenyl fragments. Although it has been reported[19] that individual valinamide carbamate compounds bearing an OCH_2 linker between their phenyl ring (*p*-Cl and *p*-CN) and amide group possess good fungicidal activities, we describe herein the synthesis and fungicidal evaluation of a series of "stretched" iprovalicarb derivatives bearing an OCH_2 or CH_2OCH_2 linker between the phenyl ring and the valinamide function of iprovalicarb. We have also shown for the first time that the introduction of a

* State Key Laboratory of Elemento-Organic Chemistry, Collaborative Innovation Center of Chemical Science and Engineering, Nankai University, Tianjin 300071, China. E-mail: zwg@nankai.edu.cn.
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propargyloxy group had a positive effect on the antioomycetic activity.

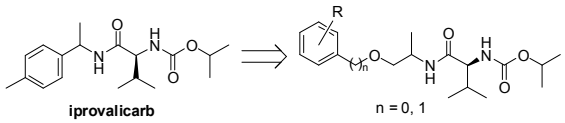
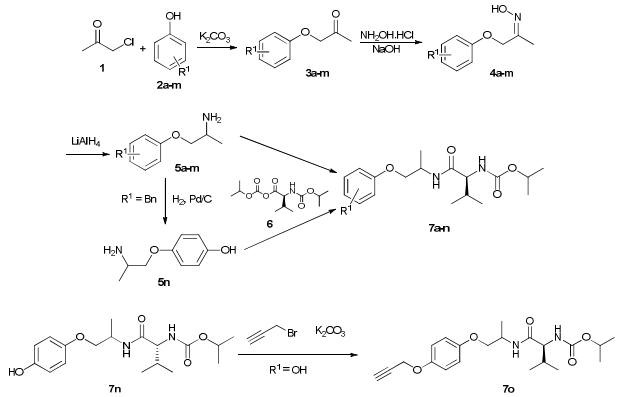


Fig. 2 Design of the target compounds

Results and discussion

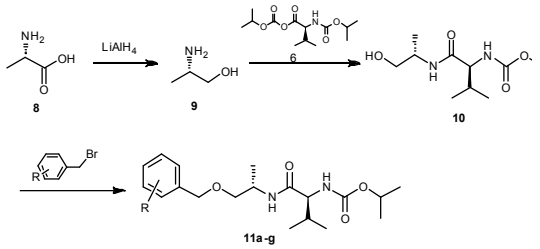
Chemistry

A series of "stretched" compounds bearing an OCH_2 linker **7a–o** was synthesized as shown in Scheme 1. The precursor compounds **3a–m**, **4a–m**, and **5a–m** were synthesized according to a previously reported procedure. All of the aryloxy acetophenones **3** were prepared by the alkylation of the corresponding substituted phenols with chloroacetone in DMF in the presence of potassium carbonate and sodium iodide. The oximes **4** were subsequently prepared by the addition of $NH_2OH{\cdot}HCl$ and NaOH to the aryloxy acetophenones **3** at room temperature. The result of a previous study showed that the hydrogenation of oximes over palladium on carbon provided facile access to the corresponding amines in high yield. However, the hydrogenation of the oximes **4** under these conditions failed to afford the corresponding amines **5**. To overcome this issue, the oximes **4** were instead reduced with $LiAlH_4$ in dry THF to give the corresponding amines **5** in good yields. Amine **5m** was subsequently debenzylated using Pd/C and H_2 to give amine **5n**. L-Valine was treated with isopropyl chloroformate under basic conditions in THF to give the mixed anhydride **6**, which was used without purification or isolation. The subsequent treatment of **6** with triethylamine and amines **5** in tetrahydrofuran gave the title compounds **7a–n** in 80–86% yields (Scheme 1). The propargylation of compound **7n** (R^1 = OH) with propargyl bromide in the presence of K_2CO_3 under reflux conditions for 10 h gave the corresponding ether **7o** (Scheme 1).



Scheme 1. Synthetic route to compounds **7a–n** and **7o**

A series of "stretched" compounds bearing a CH_2OCH_2 linker **11a–g** was synthesized as shown in Scheme 2. Aminopropanol **9** was prepared by the reduction of L-alanine with $LiAlH_4$ according to a previously reported procedure. Compound **10** was successfully prepared using the method described above for the synthesis of **7**. The subsequent alkylation of compound **10** with various benzyl bromides gave the desired products **11a–g**.



Scheme 2. Synthetic route to compounds **11a-g**

All of the synthesized compounds were characterized by ^1H and ^{13}C NMR and HR-MS. All of the spectral and analytical data were consistent with the assigned structures.

Fungicidal Activity

The *in vitro* fungicidal activities of compounds **7a–o** and **11a–g** towards *Phytophthora capsici* are shown in Table 1 (reported as EC_{50} values in μmol L^{-1}). The EC_{50} values were obtained from Petri dish trials and represent the concentrations at which the test compounds inhibited the growth of the fungus by 50%. Most of the valinamide carbamates **7** bearing an OCH_2 bridge showed excellent fungicidal activity against *Phytophthora capsici*, especially for the *para*-substituted compounds. Once again, the experimental data confirmed that the *para*-substituted compounds exhibited stronger activity than their *mete*- or *ortho*-substituted counterparts. In contrast to previously reported valinamide fungicides, the methyl- and chloro-substituted compounds prepared in the current study were not the most active examples from this series. The EC_{50} values of compounds **7f** (R = 4-CH_3) and **7i** (R = 4-CF_3) were 22.5 and 11.7 μmol L^{-1}, respectively. Compounds containing a sterically bulky alkyl group, e.g. **7h** (EC_{50} = 56.4 μmol L^{-1}), showed much lower levels of fungicidal activity. In contrast, compounds containing a halogen group showed much higher levels of fungicidal activity. The EC_{50} values of compounds **7b** (R = 4-F), **7d** (R = 4-Cl), and **7e** (R = 4-Br) were 2.06, 1.89 and 2.38 μmol L^{-1}, respectively. Compounds bearing small alkyloxy groups achieved the highest activity of all of the compounds in the valinamide family. The EC_{50} values of compounds **7j** (R = 4-OCH_3) and **7l** (R = 4-OCF_3) were 1.53 and 1.36 μmol L^{-1}, respectively. Interestingly, the introduction of a propargyloxy group at the *para*-position of the phenyl ring led to a pronounced increase in fungicidal activity. The most active compound **7o** had an EC_{50} value of 0.59 μmol L^{-1} (three-fold greater than that of the known compound **7d** (R = 4-Cl) and two-fold greater than that of compound **7l** (R = 4-OCF_3)) against *Phytophthora capsici*. The propargyloxy group has been reported to play an important role in the fungicidal activity of mandipropamide.[10] However, there have been no reports to date suggesting that the introduction of a propargyloxy group can be used as a strategy for increasing the fungicidal activity of any other CAA fungicides (i.e., valinamide carbamate and cinnamic

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Table 1. Fungicidal activities of compounds **7a–o** and **11a–g** against *Phytophthora capsici* (*in vitro*) along with their predicted activities

No.	Substituents		y = a + bx	r^2	EC_{50}	
	R^1	0			μmol L^{-1}	95% CI*
7a	H	0	y = 2.4517 + 3.6457x	0.9650	14.8	13.5-16.4
7b	*p*-F	0	y = 5.1629 + 1.2016x	0.9755	2.06	1.33-3.19
7c	*o*-F	0	y = 3.2447 + 1.8472x	0.9973	25.2	21.3-29.7
7d	*p*-Cl	0	y = 5.813 + 5.3012x	0.9857	1.89	1.11-3.26
7e	*p*-Br	0	y = 5.3748 + 5.509x	0.9937	2.38	1.04-5.47
7f	*p*-CH_3	0	y = 2.6767 + 2.6063x	0.9863	22.5	19.4-25.5
7g	*m*-CH_3	0	y = 2.9982 + 1.7720x	0.9883	38.5	32.8-45.1
7h	*p*-t-Bu	0	y = 3.1965 + 1.3407x	0.9850	56.4	44.5-71.6
7i	*p*-F_3C	0	y = 4.2399 + 1.8009x	0.9991	11.7	8.93-14.9
7j	*p*-CH_3O	0	y = 2.0601x + 5.3874	0.9733	1.53	1.01-2.32
7k	*o*-CH_3O	0	y = 3.9365 + 1.4030x	0.9835	15.6	12.1-20.2
7l	*p*-CF_3O	0	y = 5.5047 + 2.0758x	0.9776	1.36	1.17-1.57
7m	*p*-BnO	0	y = 4.9551 + 1.7729x	0.9883	2.40	2.10-2.92
7n	*p*-OH	0	y = 3.7098 + 1.0486x	0.9932	48.2	37.1-62.9
7o	*p*-$HCCCH_2O$	0	y = 9.2377 + 6.6440 x	0.9917	0.59	0.41-0.87
11a	H	1	y = -3.7477 + 5.9951x	0.9866	99.7	56.5-173
11b	*p*-F	1	y = -4.0438 + 5.6919x	1.0360	96.3	58.4-163
11c	*m* -F	1	y = 1.0083 + 2.7566x	0.9975	90.9	71.5-115
11d	*o*-F	1	y = -4.0638 + 6.2018x	0.9917	108	67.6-158
11e	*p*-Cl	1	y = -3.8533+ 4.0541x	0.9856	106	62.4-174
11f	*p*-CH_3	1	y = -4.1271 + 6.1156x	0.9565	90.4	57.5-150
11g	*p*-CF_3O	1	y = 2.1463 + 3.7225x	0.9906	15.0	11.7-19.2
	Dimethomorph		y = 9.1342 + 6.3811x	0.9349	0.59	0.49-0.80
	Iprovalicarb		y = 6.2088 + 2.1245x	0.9966	0.84	0.69-1.03

* CI: confidence interval.

Table 2. Fungicidal activities of selected compounds against *Phytophthora capsici* and *Pseudoperonospora cubensis* (*in vivo*)

No.	*P. capsici* (% control at given concentration mg L^{-1})					*P. cubensis* (% control at given concentration mg L^{-1})					cLog P
	100	50	25	12.5	6.25	100	50	25	12.5	6.25	
7b	100	100	82	80	49	81	72	61	44	40	2.89
7d	100	100	100	66	62	84	70	66	42	35	3.29
7j	100	100	88	79	21	81	70	62	54	30	2.60
7l	100	100	74	30	30	84	72	66	47	42	4.26
7m	87	35	30	30	26	78	69	58	41	37	4.34
7o	100	100	100	92	79	86	72	70	54	46	2.82
iprovalicarb	100	100	100	100	70	-*	-	-	-	-	3.20
dimethomorph	100	100	100	100	85	82	74	54	37	27	2.73

* no test.

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acid fungicides).[17, 18] This result therefore provides clear evidence that the inclusion of a propargyl group can have a pronounced impact on the fungicidal activity of valinamide carbamate derivatives, although the extent of this effect is dependent on the other substituents. Steric congestion can lead to a sharp reduction in the fungicidal activity, as demonstrated in our previous study, where steric hindrance made it difficult for a propargyl group to interact with the binding pocket of cellulose synthase.

In contrast to compounds **7a–o**, the inclusion of three linker atoms to give compounds **11a–g** appeared to be unsuitable for good fungicidal activity. Most of the compounds belonging to the latter of these two series showed poor fungicidal activity. This result could be attributed to the adverse steric effect of the CH_2OCH_2 bridge.

A further *in vivo* assay was conducted in a greenhouse to estimate the fungicidal activities of the most active compounds against *P. capsici* and *P. cubensis*. The results of our previous study[17, 18] revealed that the high cLogP values of the valinamide carbamate derivatives led to a significant decrease in their *in vivo* fungicidal potency against *P. capsici*, because of their poor absorption through the root. As shown in **Table 2**, the cLogP values of most of the compounds prepared in this study were in the range of 2.6–3.3, except for compounds **7l** and **7m** bearing trifluoromethoxy and benzyloxy moieties, respectively. Most of these compounds exhibited very good *in vivo* fungicidal activity, with a strong association between their EC_{50} value and *in vivo* fungicidal potency against *P. capsici* and *P. cubensis.* Compound **7o** displayed high levels of control of 79 and 46% against *P. capsici* and *P. cubensis* at 6.25 μg mL^{-1}, respectively, and showed higher levels of antioomycetic activity than dimethomorph (85 and 27%) and iprovalicarb (70%) at the same concentration. However, high cLogP compounds, e.g. **7l** and **7m**, showed much lower fungicidal activity for root irrigation treatments (*P. capsici*) than leaf spray (*P. cubensis*).

Interestingly, these compounds showed good broad-spectrum fungicidal activities against non-oomycete diseases at 50 μg/mL, with almost all of them inhibiting the growth of *S. sclerotiorum* by more than 90%, which was similar to that of chlorothalonil. Compound **7j** showed the highest level of activity towards *P. piricola* at 100%, which was greater than that of chlorothalonil (**Table 3**).

We subsequently determined the EC_{50} values of a selection of the synthesized compounds against a variety of different fungi, and the results are listed in **Table 4**. These compounds **7** and **11** showed fungicidal activities against *S. sclerotiorum* similar to or higher than those of the control compound Chlorothalonil (21.8 μmol L^{-1}). Compounds **7b**, **7h**, **7i**, **7j**, **7o**, **11a**, **11d**, **11e** and **11g** gave EC_{50} values of 7.28, 7.62, 11.5, 12.9, 14.7, 15.8, 16.4, 17.5 and 10.4 μmol L^{-1} against *S. sclerotiorum*, respectively. Compound **7j** also provided good levels of activity against *P. piricola* with an EC_{50} value of 9.6 μg/mL.

Table 3. Fungicidal spectrum test of selected compounds at 50 μg/mL

No.	FV[1]	CA[2]	PP[3]	AS[4]	GZ[5]	SS[6]	BC[7]	TC[8]
7a	48.1	57.1	65.0	72.7	73.1	75.0	61.0	67.2
7b	46.2	52.9	90.9	63.2	66.7	90.9	81.4	86.3
7c	42.3	35.3	100	68.4	66.7	86.4	81.4	88.2
7d	50.0	47.1	63.6	68.4	66.7	90.9	83.7	92.2
7e	47.4	36.8	68.4	63.2	53.3	90.2	76.1	88.2
7f	38.5	47.1	79.5	63.2	60.0	84.1	79.1	86.3
7g	42.3	47.1	100	63.2	66.7	88.6	83.7	92.2
7h	42.3	5.9	100	63.2	66.7	95.5	79.1	86.3
7i	46.2	41.2	100	63.2	73.3	93.2	79.1	88.2
7j	50.0	35.3	100	68.4	53.3	90.9	76.7	84.3
7k	46.2	35.3	90.9	68.4	66.7	90.9	79.1	84.3
7l	33.3	31.6	35.7	76.2	47.1	91.0	90.2	79.1
7m	33.3	36.8	44.6	71.4	38.2	90.2	76.1	68.7
7n	38.1	47.4	46.4	76.2	52.9	90.2	84.8	90.3
7o	52.4	63.2	25.0	71.4	41.2	90.2	76.1	73.1
11a	-	23.8	58.1	45.5	61.9	93.4	69.0	62.2
11b	-	23.8	58.1	50.0	59.5	90.8	66.7	58.1
11d	-	28.6	48.4	45.5	38.1	88.2	69.0	62.2
11f	-	28.6	64.5	72.7	71.4	93.4	73.8	64.9
11g	-	23.8	58.1	54.5	61.9	93.4	69.0	67.6
chlorothalonil	83	75	92	74	73	96	96	96

[1] FV: *Fusarium vasinfectum*; [2] CA: *Cercospora arachidicola;* [3] PP: *Physalospora piricola;* [4] AS: *Alternaria solani;* [5] GZ: *Gibberella zeae;* [6] SS: *Sclerotinia sclerotiorum;* [7] BC: *Botrytis cinerea;* [8] TC: *Thanatephorus cucumber;* [9] PC: *Phytophthora capsici (PC).*

Table 4. EC_{50} values of fiveteen selected compounds against four different fungi (μmol L^{-1})

No.	SS[1]	PP[2]	BC[3]	TC[4]
7b	7.28	36.1	-	
7d	22.1	-	-	16.3
7g	-	34.5	-	15.9

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7h	7.62	29.4	-	-
7i	11.5	-	-	-
7j	12.9	26.1	-	-
7l	-	-	15.8	-
7n	36.7	-	-	27.5
7o	14.7	-	-	-
11a	15.8	-	-	-
11b	25.8	-	-	-
11d	16.4	-	-	-
11e	17.5	-	-	-
11f	25.3	-	-	-
11g	10.4	-	-	-
Chlorothalonil	21.8	27.5	4.14	6.39

[1] SS: *Sclerotinia sclerotiorum;* [2] PP: *Physalospora piricola;* [3] BC: *Botrytis cinerea;* [4] TC: *Thanatephorus cucumber*.

Experimental

Materials and methods

^{1}H and ^{13}C NMR spectra were measured on a Bruker AC-P500 instrument ((Bruker, Fallanden, Switzerland) using TMS as internal standard and $CDCl_3$ as a solvent. Melting points were determined on an X-4 binocular microscope melting point apparatus (Beijing Tech Instruments, Beijing, China) and were uncorrected. HRMS were recorded on an Ionspec 7.0-T Fourier-transform ion-cyclotron resonance (FTICR) mass spectrometer (Bruker, Billerica, USA). All of the reagents were purchased as the analytical grade.

General procedure for the synthesis of the 1-substituted phenoxypropan-2-ones 3a–m. The intermediate phenoxypropan-2-ones were prepared according to a previously reported method by the reaction of the corresponding substituted phenols with α-chloroacetone.[20] Analytical data for the characterization of compounds **3a–m** can be found in the Supporting Information.

General synthetic procedure for the synthesis of 1-substituted phenoxypropan-2-one oximes 4a–m. The intermediate oximes were prepared according to a previously reported method by the reaction of the corresponding ketone **3** with hydroxylamine hydrochloride.[21] Analytical data for the characterization of compounds **4a–m** can be found in the Supporting Information.

General procedure for the synthesis of the 1-substituted phenoxypropan-2-amines 5a–m. Lithium aluminium hydride (45.3 mmol) was suspended in 50 mL of ether at 0 °C. Oxime **4** (18.1 mmol) was then added to the mixture in small portions, and the resulting mixture was heated at reflux for 3 h. The mixture was then cooled to room temperature and slowly treated with a 2 N NaOH solution. The mixture was subsequently filtered and evaporated to dryness to give a yellow residue, which was purified by flash column chromatography. Analytical data for the characterization of compounds **5a–m** can be found in the Supporting Information.

Procedure for the synthesis of the 4-(2-aminopropoxy)phenol (5n). Amine **5m** (2.0 g, 7.78 mmol) was dissolved in 50 mL of ethanol, and the resulting solution was flushed with N_2. Palladium on carbon (0.2 grams, 10% wt) was added to the solution, and the resulting mixture was hydrogenated under 15 atm of H_2 pressure for 12 h. The mixture was then filtered to remove the catalyst, and the filtrate was concentrated under vacuum to afford a yellow residue, which was purified by flash column chromatography to give the desired product (0.95 g, 73.1%. M.p.: 72–74 °C.

General procedure for the synthesis of the isopropyl ((2S)-3-methyl-1-oxo-1-((1-substituted phenoxypropan-2-yl)amino)butan-2-yl)carbamates 7a–n. 4-Methylmorpholine (6 mmol) was added to a solution of (S)-2-((isopropoxycarbonyl)amino)-3-methylbutanoic acid (5 mmol) in anhydrous tetrahydrofuran (20 mL), followed by ethyl chloroformate (5 mmol), and the resulting mixture was stirred at 0 °C for 1 h. A solution of amine **5** (6 mmol) in anhydrous tetrahydrofuran (10 mL) was then added to the reaction in a drop-wise manner, and the resulting mixture was stirred at room temperature for 10 h. The reaction mixture was then filtered and the filtrate concentrated under vacuum to give a residue, which was extracted with ethyl acetate (3 × 20 mL). The combined organics were washed with brine (2 × 15 mL), dried over anhydrous sodium sulfate, and concentrated *in vacuo* to give the crude product, which was purified by flash column chromatography to give the desired product **7a** as a white solid (78.5%). M.p.: 89–91 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.23 (m, 2H, Ar-*H*), 7.04–6.85 (m, 3H, Ar-*H*), 6.25 (t, *J* = 8.6 Hz, 1H, CHCON*H*), 5.24 (dd, *J* = 25.3, 8.1 Hz, 1H, OCON*H*), 4.89 (dt, *J* = 12.4, 6.1 Hz, 1H, OC*H*$(CH_3)_2$), 4.41 (d, *J* = 3.3 Hz, 1H, CH_2CHCH_3), 3.95 (qd, *J* = 9.4, 4.4 Hz, 3H, OCONHC*H* + OCH_2), 2.26–2.00 (m, 1H, CHC*H*$(CH_3)_2$), 1.33 (dd, *J* = 6.8, 3.4 Hz, 3H, CHCH_3), 1.23 (dd, *J* = 8.1, 6.4 Hz, 6H, OCH(C$H_3)_2$), 1.03–0.84 (m, 6H, CHCH(C$H_3)_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.66, 158.50, 156.28, 129.46, 121.13, 114.73, 70.30, 68.60, 60.37, 44.71, 31.07, 22.07, 19.24, 17.59; HRMS (MALDI) *m/z* Calcd for $C_{18}H_{28}N_2O_4Na^+$ $[M + Na]^+$ = 359.1941, found 359.1945.

Analytical data for the characterization of compounds **7b–n** can be found in the Supporting Information.

Procedure for the synthesis both diastereoisomers of isopropyl ((2S)-3-methyl-1-oxo-1-((1-(4-(prop-2-yn-1-yloxy)phenoxy)propan-2-yl)amino)butan-2-yl)carbamate (7o). To a solution of compound **7n** (2.83 mmol) in dry acetone (30 mL) was added anhydrous K_2CO_3 (4.26 mmol), and the resulting mixture was stirred for 1 h. Propargyl bromide (4.3 mmol) was then added to the mixture in a drop-wise manner over 30 min, and the resulting mixture was heated at reflux for 10 h. The reaction mixture was then cooled to ambient temperature, filtered, and evaporated to dryness to give a brown oily residue. The residue was dissolved in methylene chloride and washed with water (2 × 50 mL). The organic layer was then dried over anhydrous Na_2SO_4 and evaporated under vacuum to give the crude product, which was purified by flash column chromatography to give diastereoisomer **7o** as a white solid (80.9%). M.p.: 81–83 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.90–6.69 (m, 4H, Ar-*H*), 6.03 (s, 1H, CHCON*H*), 5.08 (s, 1H, OCON*H*), 4.90–4.73 (m, 1H, OC*H*$(CH_3)_2$), 4.57 (d, *J* = 1.9 Hz, 2H, HCCCH_2), 4.29 (s, 1H, CH_2CHCH_3), 3.82 (dd, *J* = 13.8, 6.6 Hz, 3H, OCONHC*H* +

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OCH_2), 2.44 (s, 1H, OCH_2CCH), 2.06 (s, 1H, $CHCH(CH_3)_2$), 1.24 (d, J = 6.8 Hz, 3H, $CHCH_3$), 1.15 (t, J = 6.2 Hz, 6H, $OCH(CH_3)_2$), 0.92–0.77 (m, 6H, $CHCH(CH_3)_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.95, 156.30, 153.37, 152.06, 116.13, 115.39, 78.82, 75.41, 71.02, 68.58, 60.26, 56.54, 44.68, 31.37, 21.96, 19.18, 17.56; HRMS (MALDI) *m/z* Calcd for $C_{21}H_{30}N_2O_5Na^+$ $[M + Na]^+$ = 413.2047, found 413.2049.

Procedure for the synthesis of (S)-2-aminopropan-1-ol (9). The intermediate amino alcohol **9** was prepared according to a previously reported method by the reduction reaction of L-alanine with $LiAlH_4$.[22]

Procedure for the synthesis of isopropyl ((S)-1-(((S)-1-hydroxypropan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)carbamate (10). Intermediate **10** was prepared according to the procedure reported in chapter 2.2.6 to give a white solid (82.1%). M.p.: 179–181 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.37 (d, J = 6.8 Hz, 1H, CHCONH), 5.31 (d, J = 7.4 Hz, 1H, OCONH), 5.02–4.77 (m, 1H, $OCH(CH_3)_2$), 4.09 (dt, J = 10.9, 6.8 Hz, 1H, CH_2CHCH_3), 3.93 (dt, J = 9.8, 5.0 Hz, 1H, OCONHCH), 3.69 (dd, J = 11.1, 3.6 Hz, 1H, OCH_2CH), 3.56 (dd, J = 11.1, 5.8 Hz, 1H, OCH_2CH), 2.59 (s, 1H, OH), 2.12 (d, J = 6.6 Hz, 1H, $CHCH(CH_3)_2$), 1.26 (dd, J = 6.2, 3.6 Hz, 6H, $OCH(CH_3)_2$), 1.21 (d, J = 6.9 Hz, 3H, $CHCH_3$), 1.04–0.93 (m, 6H, $CHCH(CH_3)_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.97, 156.51, 68.84, 66.65, 60.61, 47.83, 30.88, 22.06, 19.26, 17.95, 16.86; HRMS (ESI) *m/z* Calcd for $C_{12}H_{25}N_2O_4^+$ $[M + H]^+$ = 261.1809, found 261.1810.

Procedure for the synthesis of isopropyl ((S)-1-(((S)-1-(substituted benzyloxy)propan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)carbamate (11). To a stirred suspension of NaH (0.23 g, 0.57 mmol, 60%) in DMF (10 mL) was added intermediate **10** (1.0 g, 3.8 mmol) in a portion-wise manner at −10 °C, and the resulting mixture was stirred for 20 mins at −10 °C. A solution of benzyl bromide (5.7 mmol) in DMF (10 mL) was then added to the reaction in a drop-wise manner over 30 mins at −10 °C, and the resulting mixture was stirred for 6 h at the same temperature. The mixture was then poured into 200 mL of ice water to give a white solid, which was collected by filtration and purified by recrystallization from ethanol to give compound **11a** as a white solid (68.9%). M.p.: 145–147 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49–7.19 (m, 5H, Ar-H), 6.12 (s, 1H, CHCONH), 5.23 (s, 1H, OCONH), 4.90 (s, 1H, $OCH(CH_3)_2$), 4.53 (s, 2H, Ar-CH_2), 4.22 (s, 1H, CH_2CHCH_3), 3.91 (s, 1H, OCONHCH), 3.43 (s, 2H, OCH_2CH), 2.08 (s, 1H, $CHCH(CH_3)_2$), 1.23 (t, J = 7.2 Hz, 9H, $CHCH_3$ + $OCH(CH_3)_2$), 1.01–0.87 (m, 6H, $CHCH(CH_3)_2$); ^{13}C NMR (101 MHz, CDCl3) δ 170.65, 156.27, 137.99, 128.43, 127.75, 127.66, 73.17, 72.84, 68.50, 60.30, 44.96, 31.24, 22.09, 19.18, 17.70; HRMS (ESI) *m/z* Calcd for $C_{19}H_{31}N_2O_4^+$ $[M + H]^+$ = 351.2278, found 351.2277.

Analytical data for the characterization of compounds **7b–g** can be found in the Supporting Information.

Fungicidal Activities

***In vitro* Fungicidal activity.** The *in vitro* fungicidal activities of the synthesized compounds were evaluated against *Fusarium vasinfectum (FV), Cercospora arachidicola (CA), Physalospora piricola (PP), Alternaria solani (AS), Gibberella zeae (GZ), Sclerotinia sclerotiorum (SS), Botrytis cinerea (BC),* and *Thanatephorus cucumber (TC)*, as previously described.[17, 23-25] The results of these analyses are summarized in Tables 3 and 4.

Fungicidal activity against *Phytophthora capsici* (*in vivo*). The *in vivo* fungicidal activities of the synthesized compounds against *P. capsici* were determined as previously described.[17, 26] The results are summarized in Table 1.

Fungicidal activity against *Pseudoperonospora cubensi* (*in vivo*). The *in vivo* fungicidal activities of the synthesized compounds against *P. capsici* were determined as previously described.[17, 27] The results are summarized in Table 2.

Conclusions

In summary, we have designed and synthesized a series of 1-substituted phenoxypropan-2-amino valinamide carbamates as potential cellulose synthase inhibitors. The subsequent evaluation of the fungicidal activities of these compounds revealed that the introduction of an additional OCH_2 linker into iprovalicarb resulted in very good levels of fungicidal activity against *Phytophthora capsici* and *Pseudoperonospora cubensis*. Most interestingly, the introduction of a propargyloxy group led to a considerable increase in the fungicidal activity of the "stretched" iprovalicarb. Compound **7o** was identified as the most promising candidate based on its excellent fungicidal potency against oomycete diseases and good fungicidal activity against non-oomycete diseases. Further studies are currently underway in our laboratory involving field trials.

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Notes and references

1 W. Krämer, U. Schirmer, P. Jeschke and M. Witschel, Modern Crop Protection Compounds, Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim 2012.
2 Y. Miyake, J. Sakai, I. Miura, K. Nagayama and M. Shibata, The BCPC International Congress: Crop Science and Technology, Volumes 1 and 2. Proceedings of an international congress held at the SECC, Glasgow, Scotland, UK, 10-12 November, 2003.
3 R. P. K. Stenzel, T. Seitz, and A. W. R. Tiemann, Brighton Crop Protection Conference. Pests and Diseases, 1998.
4 G. Agosteo, E. Marsilii, A. Pane, C. Rizza, F. Raudino, S. Cacciola, A. Giambelli and G. d. San Lio, Strategie innovative di difesa nel settore ortoflorofrutticolo, Torino, Italia, 3-4 Marzo 2010.
5 Fungicide Resistance Action Committee, FRAC Code List 2016, 2016, http://www.frac.info/docs/default-source/publications/frac-code-list/frac-code-list-2016.pdf?sfvrsn=2.
6 M. Blum, M. Boehler, E. Randall, V. Young, M. Csukai, S. Kraus, F. Moulin, G. Scalliet, A. O. Avrova, S. C. Whisson and R. Fonne-Pfister, *Mol. Plant Pathol.*, 2010, **11**, 227-243.

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DOI: 10.1039/C6RA17908H

7 M. Blum, H. A. Gamper, M. Waldner, H. Sierotzki and U. Gisi, *Fungal Biol.*, 2012, **116**, 529-542.
8 D. Hermann, D. W. Bartlett, W. Fischer and H. J. Kempf, The BCPC International Congress: Crop Science & Technology, Glasgow, Scotland UK, 31 October-2 November, 2005.
9 C. Lamberth, A. Jeanguenat, F. Cederbaum, A. De Mesmaeker, M. Zeller, H. Kempf and R. Zeun, *Bioorg. Med. Chem.*, 2008, **16**, 1531-1545.
10 C. Lamberth, A. Jeanguenat, H. Kempf, M. Zeller and R. Zeun, *Pest. Manag. Sci.*, 2006, **62**, 446-451.
11 C. Lamberth, H. J. Kempf and M. Križ, *Pest Manag. Sci.*, 2007, **63**, 57-62.
12 S. J. Yu, C. Zhu, Q. Bian, C. Cui, X. J. Du, Z. M. Li and W. G. Zhao, *Acs Comb. Sci.*, 2014, **16**, 17-23.
13 N. Su, Z. J. Wang, L. Z. Wang, X. Zhang, W. L. Dong, H. X. Wang, Z. M. Li and W. G. Zhao, *Chem. Biol. Drug Design*, 2011, **78**, 101-111.
14 H. H. Li, Z. J. Wang, L. Z. Wang, Z. M. Li and W. G. Zhao, *Chem. J. Chin. Univ.*, 2011, **32**, 79-83.
15 S. Li, C. Cui, M. Y. Wang, S. J. Yu, Y. X. Shi, X. Zhang, Z. M. Li, W. G. Zhao and B. J. Li, *J Fluorine Chem.*, 2012, **137**, 108-112.
16 H. W. Yao, H. H. Li, N. N. Su, H. X. Wang, X. H. Liu, L. Z. Wang, X. Zhang, Z. M. Li and W. G. Zhao, *Chem. J. Chin. Univ.*, 2009, **30**, 908-912.
17 X. J. Du, Q. Bian, H. X. Wang, S. Yu, J. J. Kou, Z. P. Wang, Z. M. Li and W. G. Zhao, *Org. Biomol. Chem.*, 2014, **12**, 5427-5434.
18 Z. P. Wang, J. J. Kou, Y. Gao, X. J. Du, Y. H. Li and W. G. Zhao, *RSC Adv.*, 2015, **5**, 100418–100423.
19 M. Shibata, K. Sugiyama, N. Yonekura, J. Sakai, Y. Kojima and S. Hayashi, *United States Patent US*, 1996, **5574064**.
20 M. del Carmen Cruz and J. Tamariz, *Tetrahedron*, 2005, **61**, 10061-10072.
21 K. Huang, M. Ortiz-Marciales, V. Stepanenko, M. De Jesús and W. Correa, *J. Org. Chem.*, 2008, **73**, 6928-6931.
22 D. Z. Feng, Y. L. Song, X. H. Jiang, L. Chen and Y. Q. Long, *Org. Biomol. Chem.*, 2007, **5**, 2690-2697.
23 N. N. Su, L. X. Xiong, S. J. Yu, X. Zhang, C. Cui, Z. M. Li and W. G. Zhao, *Comb. Chem. High. T. Scr.*, 2013, **16**, 484-493.
24 J. Xu, X. Zhao, X. Han and Y. Du, *Pest. Biochem. Physiol.*, 2007, **87**, 220-228.
25 S. Mitani, S. Araki, T. Yamaguchi, Y. Takii, T. Ohshima and N. Matsuo, *Pest. Biochem. Physiol.*, 2001, **70**, 92-99.
26 J. Andrés Ares, A. Rivera Martínez and J. Fernández Paz, *Span. J. Agri. Res.*, 2005, **3**, 429-436.
27 M. Li, C. L. Liu, L. Li, H. Yang, Z. N. Li, H. Zhang and Z. M. Li, *Pest Manag. Sci.*, 2010, **66**, 107-112.