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Design, synthesis, and fungicidal activity of novel carboxylic acid amides represented by N-benzhydryl valinamode carbamates

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Carboxylic Acid Amide (CAA) fungicides are an important class of agricultural fungicide with oomycete activity and low toxicity toward mammalian cells. To find CAA analogues with high activity against resistant pathogens, a series of substituted *N*-benzhydryl valinamide carbamate derivatives were designed and synthesized by introducing substituted aromatic rings into valinamide carbamate leads. Bioassays showed that some title compounds exhibited very good *in vitro* fungicidal activity against *Phytophthora capsici* and *in vivo* fungicidal activities against *Pseudoperonospora cubensis*. Topomer CoMFA was performed to explore the structure–activity relationship on the basis of the *in vitro* data. The dimethoxy substituted aromatic analogue **9e** was found to display higher *in vitro* fungicidal activitiy against *Phytophthora capsici* than iprovalicarb but lower activity than mandipropamid, and higher *in vivo* fungicidal activity against *Pseudoperonospora cubensis* than dimethomorph at a dosage of 6.25 μg mL^{-1}.

Introduction [1]

Oomycetes are biologically and biochemically distinct from ascomycetes,[1] and exposure to the former 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 downy grape mildew. Carboxylic acid amide (CAA) fungicides exhibit high levels of activity against most foliar oomycete plant pathogens, such as *Plasmopara viticola* in grapes, *Phytophthora infestans* in potatoes and tomatoes, and *Pseudoperonospora cubensis* in cucurbits. CAA fungicides were officially announced by the Fungicide Resistance Action Committee (FRAC) in 2005[1] because they exhibited a common cross resistance pattern to the vast majority of *Plasmopara viticola*. CAA fungicides can be divided into three different sub-classes based on differences in their structure, including (1) cinnamic acid amides, such as dimethomorph,[2] flumorph,[3] and pyrimorph;[4] (2) valinamide carbamates, such as benthiavalicarb,[5] benthiavancarb-isopropyl, iprovalicarb,[6] and valiphenal;[7] and (3) mandelic acid amides, such as mandipropamid[8] (**Figure 1**). Although the first CAA fungicides have been routinely used for the last 20 years, their mode of action was not elucidated until 2010. In 2010, Blum et al.[9, 10] reported that both of the known mutations in the *PiCesA3* gene of *P. infestans*, which is known to be involved in the synthesis of cellulose, resulted in a change to the same amino acid residue (glycine-1105) in the protein, and that these mutations were responsible for the mandipropamid-insensitive phenotype. Furthermore, these mutants showed reduced sensitivity to compounds belonging to all CAA sub-classes. Several other mutant pathogen species have recently been report in the literature that are resistant to CAA fungicides.[9, 11-13] Changes to G1105V, G1105W or G1105S have been reported to be responsible for CAA-resistance in *Ps. cubensis*[11] and *P. viticola,*[14] respectively. The CAA compounds exert their fungicidal activity by targeting cellulose synthases in the oomycetes.

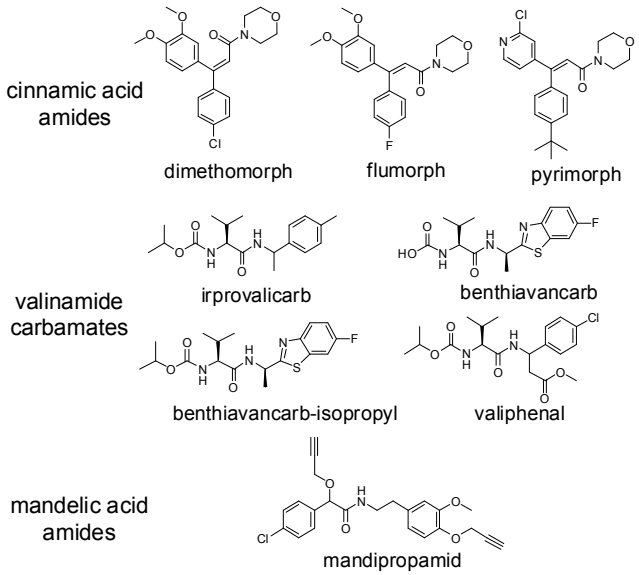

Fig. 1 Structures of commercial CCA fungicides

In previous studies,[15-18] we reported the synthesis and evaluation of the fungicidal activities of a series of mandelic acid amide derivatives. Our attempts to optimize the aromatic

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substituents as well as the structural features of the core scaffold did not lead to significant improvements in the fungicidal activities of these derivatives. Although dimethomorph was the first CAA fungicide to be introduced in 1988, followed by iprovalicarb in 1998, to date only two other cinnamic acid amide compounds (flumorph and pyrimorph) and two other valinamide carbamate compounds (benthiavalicarb and valiphenal) have progressed through development to be marketed as commercial products. The two pairs of compounds are very similar to those of dimethomorph and iprovalicarb, respectively.

In spite of differences in their overall structures, compounds belonging to all three sub-classes possess very similar structural fragments, including amide, halobenzene (or methylbenzene) and/or dialkoxy benzene moieties (**Figure 2**). Compounds belonging to the cinnamic acid amide and mandelic acid amide sub-classes possess all three of these active structural fragments, whereas compounds belonging to the valinamide carbamate sub-class only contain two of these active structural fragments. With this in mind, we became interested in synthesizing and evaluating the fungicidal activities of valinamide carbamate analogues that contained all three of the active structural fragments.

Herein, we describe the synthesis and evaluation of the fungicidal activities of a series of novel substituted *N*-benzhydryl valinamide carbamate derivatives, and show that these compounds display promising antioomycetic activity.[19] Stiez and colleagues have reported a series of monoalkoxy substituted derivatives.[20]

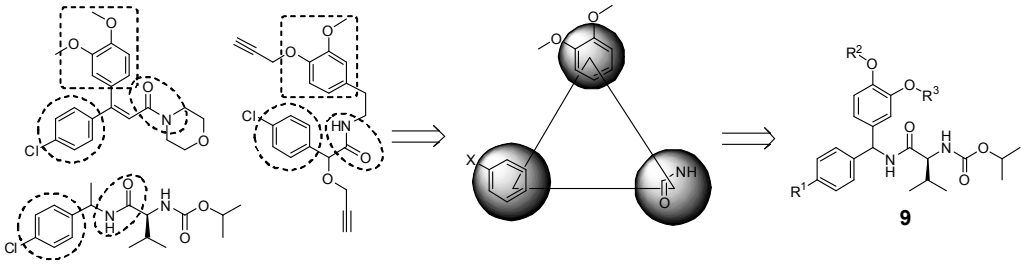
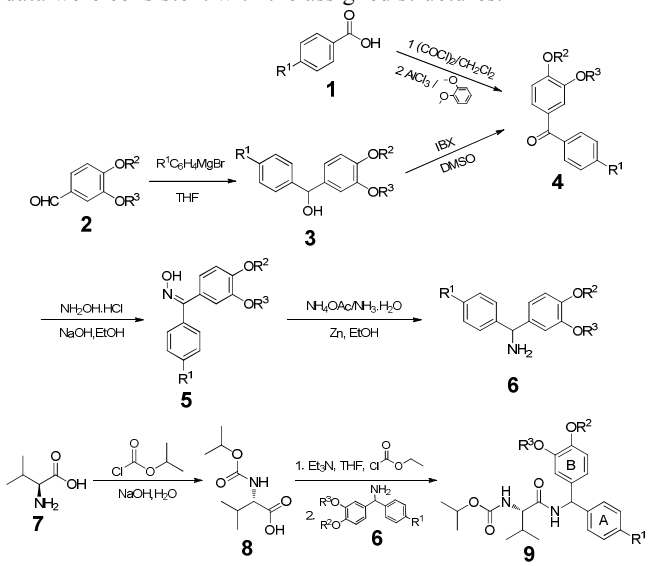


Figure 2. The common structural fragments of CCA fungicides

Results and discussion

Chemistry

Compounds **9a-v** were synthesized as shown in **Scheme 1**. The precursor compounds **4a-g** (R^2 , R^3 = Me) were synthesized according to a previously described procedure.[13] The substituted benzoyl chlorides were obtained by treating the corresponding benzoic acids **1a-g** with oxalyl chloride in the presence of a catalytic amount of *N,N*-dimethylformamide. The benzoyl chlorides were then subjected to a Friedel–Crafts acylation reaction with 1,2-dimethoxybenzene in the presence of $AlCl_3$ to give the ketone products **4a-g**. Several other compounds **4h-v** (where R^2 or R^3 were not Me) were obtained by the oxidation of the corresponding diphenylmethanols **3h-v** with IBX in dimethylsulfoxide. Compounds **3h-v** were obtained by the reaction of the substituted vanillin compounds **2h-v** with the appropriate aryl Grignard reagent. The condensation of **4a-v** with hydroxylamine hydrochloride gave the corresponding oximes **5a-v** in excellent yield. The oximes **5a-5v** were selectively reduced to the corresponding amines **6a-v** using zinc dust and ammonium formate. These reduction conditions were used instead of hydrogenation over Pd/C to avoid the loss of chlorine from the phenyl ring. The addition of isopropyl chloroformate to a solution of L-valine **7** in aqueous sodium hydroxide gave isopropyloxycarbonyl-L-valine **8** in good yield. The carboxylic acid moiety in compound **8** was then treated with ethyl chloroformate under basic conditions in tetrahydrofuran to give the mixed anhydride, which was not isolated. Subsequent treatment with triethylamine and amines **6a-v** in tetrahydrofuran gave the title compounds **9a-v** in 85–95% yield. 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.



Scheme 1. The synthetic route to compounds **9a-v**

Fungicidal Activity.

The *in vitro* fungicidal activities of compounds **9a-v** towards *Phytophthora capsici* are shown in **Table 1** (reported as EC_{50} values in μg mL^{-1}). The EC_{50} values were obtained from petri dish trials and represent the concentrations at which the tested compounds showed 50% inhibitory activity. Some compounds showed very good fungicidal activity against *Phytophthora capsici* and structure-activity relationship analysis indicated

that the substituents on the benzene ring had a significant effect on the fungicidal activity. It was clear from the data that compounds containing small alkyl groups at the *para*-position of ring A (e.g. **9e**, R^1 = Me), gave high levels of fungicidal activity against *Phytophthora capsici* (EC_{50} = 0.15 μg mL^{-1}), when ring B was a dimethoxyphenyl. Furthermore, compound **9e** showed higher antioomycetic potency than iprovalicarb (EC_{50} = 0.27 μg mL^{-1}) and a level of potency very similar to that of dimethomorph (EC_{50} = 0.12 μg mL^{-1}), but it was less active than mandipropamid (EC_{50} = 0.04 μg mL^{-1}). The *para*-methoxy derivative **9g** (EC_{50} = 0.52 μg mL^{-1}), unsubstituted derivative **9a** (EC_{50} = 0.89 μg mL^{-1}) and *para*-fluoro derivative **9b** (EC_{50} = 1.19 μg mL^{-1}) all possessed interesting levels of fungicidal activity. It is noteworthy, however, that compounds containing a large and sterically bulky halogen or alkyl group, e.g. **9d** (EC_{50} = 139.4 μg mL^{-1}) and **9f** (EC_{50} = 234.1 μg mL^{-1}), showed much lower levels of fungicidal activity.

Table 1. Fungicidal activity against *Phytophthora capsici* (*in vitro*) and predicted activities of the title compounds **9**

No.	Substituents			y = a + bx	r^2	EC_{50} (95% confidence interval) μg mL^{-1}	pEC_{50} μg mL^{-1}	
	R^1	R^2	R^3				Exp.	Calcd**.
9a	H	Me	Me	y = 5.0599 + 1.1453x	0.9662	0.89 (0.65-1.21)	6.05	5.94
9b	F	Me	Me	y = 4.8445 + 2.0197x	0.9817	1.19 (1.00-1.32)	5.92	5.48
9c	Cl	Me	Me	y = 4.2690 + 0.7323x	0.9729	9.14 (6.31-13.25)	5.04	4.82
9d	Br	Me	Me	y = 2.5569 + 1.1393x	0.9954	139.4 (109.0-178.4)	3.86	4.79
9e*	Me	Me	Me	y = 5.6249 + 0.7524x	0.9692	0.15 (0.06-0.35)	6.83	5.95
9f	*t*-Bu	Me	Me	y = 1.1442 + 1.5007x	0.9925	234.1 (181.4-302.1)	3.63	3.27
9g	MeO	Me	Me	y = 5.9592 + 3.3480x	0.9719	0.52 (0.46-0.58)	6.29	5.97
9h	H	Et	Me	y = 5.5692 + 2.0599x	0.9710	0.53 (0.46-0.61)	6.28	5.60
9i	F	Et	Me	y = 3.9643 + 1.0324x	0.9871	10.07 (7.76-13.08)	4.50	5.14
9j	Cl	Et	Me	y = 2.3445 + 1.2400x	0.9983	147.8 (116.7-187.1)	3.83	4.48
9k	Me	Et	Me	y = 2.1691 + 1.2624x	0.9918	174.8 (136.3-224.1)	3.76	3.96
9l	Me	propargyl	Me	y = 1.9304 + 1.5246x	0.9804	102.18 (86.2-123.3)	3.99	3.91
9m	F	Benzyl	Me	y = 2.6194 + 1.0414x	0.9988	193.2 (141.7-263.3)	3.71	4.33
9n	Cl	Benzyl	Me	y = 1.8955 + 1.3721x	0.9911	183.1 (144.4-232.1)	3.73	3.68
9o	Br	Benzyl	Me	y = 2.3025 + 1.1610x	0.9976	210.6 (156.7-282.9)	3.67	3.65
9p	Me	Benzyl	Me	y = 3.8242 + 0.4946x	0.9982	238.3 (184.9-306.6)	3.54	3.16
9q	H	Me	Et	y = 4.4663 + 0.7331x	0.9568	5.35 (3.33-8.57)	5.27	5.68
9r*	F	Me	Et	y = 1.5614 + 1.5529x	0.9744	163.85 (133.8-200.5)	3.79	5.22
9s*	Cl	Me	Et	y = 3.6425 + 0.8646x	0.9930	37.16 (23.9-57.7)	4.43	4.56
9t*	Br	Me	Et	y = 4.6247 + 1.2712x	0.9998	1.97 (1.39-2.80)	5.71	4.55
9u	Me	Me	Et	y = 2.3287 + 1.3014x	0.9912	112.9 (91.8-138.9)	3.95	4.05
9v	Me	Me	Benzyl	y = 2.1550 + 1.2509x	0.9782	188.1 (144.9-244.0)	3.72	3.43
	dimethomorph			y = 6.5558 + 1.6550x	0.9930	0.12 (0.10-0.24)		
	iprovalicarb			y = 6.2088 + 2.1245x	0.9966	0.27 (0.22-0.33)		
	mandipropamid			y = 8.4774 + 2.2311x	0.9685	0.04 (0.03-0.06)		

* testing set. ** predicted were using Topomer CoMFA.

Compounds with a large group at the *para*- or *meta*- position of ring B showed lower levels of antioomycetic activity than compounds with smaller groups at the same position, as shown in **Table 1**. The dimethoxy phenyl ring (ring B) provided the highest activity for the compounds tested in the *N*-benzhydryl valinamide carbamate sub-class. When $R^2 \neq$ Me, the optimum ring A was found to be an unsubstituted phenyl ring (R^1 = H). Compound **9h** (R^1 = H, R^2= Et) was the most active derivative with EC_{50} = 0.53 μg mL^{-1}. Compound **9i** (R^1 = F, R^2= Et) was the next most active analogue (EC_{50} = 10.07 μg mL^{-1}). Substitution at the *para*-position with larger substituents again had a negative effect on the fungicidal activity, indicating that the SAR at this position is particularly tight. Further increasing the bulk of the substituent at the *para*-position of ring B or ring A led to a significant decrease in fungicidal activity (compounds **9j-p** all gave EC_{50} values > 100 μg mL^{-1}).

In contrast, the use of bulkier groups at the *meta*-position of ring B appeared to be reasonably well tolerated, with only a relatively small drop in activity. For example, compound **9q** (R^1 = H, R^2 = Me, R^3 = Et) gave an EC_{50} value of 5.35 μg mL^{-1}, although the activity of this compound was 10-fold

weaker than that of its *para*-ethoxy substituted counterpart **9h**. Surprisingly, the *para*-bromo compound **9t** (R^1 = Br; EC_{50} = 1.97 μg mL^{-1}) showed the highest fungicidal activity of the compounds containing a halogen at this position with the order of fungicidal activity being Br > Cl > F. This trend was in complete contrast to what had been observed above. The results of the current study appear to suggest that when R^2 is methyl, the introduction of an ethyl group at the *meta*-position of ring B (i.e., R^3 = Et) could have a significant steric effect that could lead to a change in the binding mode of the substrates to the target enzyme.

A further *in vivo* assay was conducted in a greenhouse to estimate the fungicidal activities of the most active compounds against *Phytophthora capsici* and *Pseudoperonospora cubensi*. As shown in **Table 2**, the compounds showed lower levels of *in vivo* fungicidal activity against *Phytophthora capsici* than the control compounds dimethomorph and iprovalicarb. Under equivalent dosage conditions of 50 mg L^{-1}, compounds **9b**, **9g** and **9h** show 100% inhibition against *Phytophthora capsici*, whereas compound **9e**, which was identified as the most potent compound from the *in vitro* fungicidal assay, showed a slightly lower level of inhibition (96%). The activities of these compounds against *Phytophthora capsici* were therefore measured using dose reduction with serial two-fold dilution. The fungicidal activities of all of the test compounds became progressively lower against *Phytophthora capsici* at concentrations of 25 and 12.5 μg mL^{-1}, whereas the control compounds still showed 100% inhibition at these concentrations. The fungicidal activity of most potent synthesized compound **9g** decreased significantly with decreasing concentration, although its potency (83%) was greater than that of the reference dimethomorph (63%) and iprovalicarb (46%) at the 3.125 μg mL^{-1} concentration.

Table 2. Fungicidal activity against *Phytophthora capsici* and *Pseudoperonospora cubensi* (*in vivo*)

No.	*P. capsici* (% control at given concentration mg L^{-1})					*P. cubensi* (% control at given concentration mg L^{-1})					clog P
	50	25	12.5	6.25	3.125	100	50	25	12.5	6.25	
9a	87	77	59	55	37	79	59	56	42	39	3.94
9b	100	83	75	33	17	85	83	79	51	23	4.09
9e	96	63	46	38	33	88	87	77	72	71	4.44
9g	100	96	91	87	83	77	68	65	56	49	3.86
9h	100	83	61	35	30	73	58	51	47	31	4.47
9t	83	66	53	36	17	77	72	59	50	30	5.33
dimethomorph	100	100	100	87	63	82	74	69	61	47	2.73
iprovalicarb	100	100	100	71	46	-	-	-	-	-	3.2

The introduction of a second phenyl ring into the lead compounds led to a significant increase in their clogP values. The high LogP values represents a major stumbling block for drug absorption through the root. With this in mind, we calculated the LogP values (octanol/water) of the test compounds using Sybyl, and the results are shown in **Table 2**.

The results show that the *in vivo* fungicidal activities are related to their clogP values. For example, compound **9g** (clogP = 3.86) exhibited 83% inhibition down to a dose of 3.125 mg L^{-1}, whereas compounds **9e** (clogP = 4.44) and **9h** (clogP = 4.47) exhibited inhibition values of 33% and 30% at the same dose levels, respectively.

The solubilities of compounds **9e** and **9g** were also tested in water at pH 7. The results revealed that compounds **9e** (0.2 mg L^{-1}) and **9g** (1.3 mg L^{-1}) were poorly soluble in water. The aqueous solubilities of the compounds provided some understanding as to why they exhibited low *in vivo* fungicidal activities at high assay doses.

Compound **9e** did not exhibit high levels of *in vivo* fungicidal activity at all doses tested. Compound **9g** exhibited higher *in vivo* fungicidal effects than the control compounds at low dose (3.125 mg L^{-1}). However, compound **9g** did not show 100% inhibition activity at 25 mg L^{-1}.

It was envisaged that the more lipophilic compounds would be tightly bound to the leaf's waxy layer. This would allow these compounds to provide a highly effective, weatherproof and long-lasting barrier to disease by foliar sprays. Most of the compounds in **Table 2** exhibited very good inhibition against *Pseudoperonospora cubensi*. A comparison of all of the test compounds revealed a strong positive correlation between the EC_{50} values estimated for the *in vitro* fungicidal activity against *Phytophthora capsici* and the *in vivo* fungicidal activity against *Pseudoperonospora cubensi*. Compounds **9e** and **9g** displayed significant levels of control of 71 and 49% against *Pseudoperonospora cubensi* at 6.25μg mL^{-1}, respectively, and showed higher levels of antioomycetic activity than dimethomorph (47 %) at the same concentration.

Tomoper CoMFA Analysis

To further explore the influence of the different substituents on the benzhydryl group on the activities of the compounds,

we used a topomer CoMFA method to develop a deeper understanding of the quantitative structure-activity relationships. The topomer CoMFA method provides a means for an alignment-independent 3D-QSAR approach,[21] which is a more rational way to explain the hypothesis as it does not involve alignment, and it provides a means for automated activity searches in fragment libraries. In this topomer CoMFA study, we designated a training set of 18 compounds by fragmenting the molecules into three parts: valinamide carbamates, halobenzene (or methylbenzene) and dialkoxy benzene moieties, topologically aligned R1 and R2 fragments as shown in **Figure 3**.

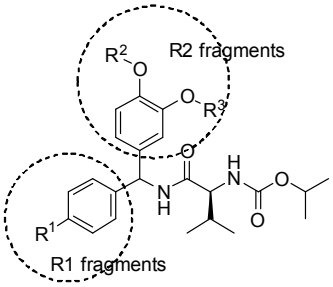


Figure 3. Diagram of split title compounds into three pieces for the topomer CoMFA modeling.

The topomer CoMFA model gives both statistical and graphical results. Statistically, the conventional non-cross-validated correlation coefficient, r^2 of 0.82 using 2 PLS components, while the cross-validation gave a q^2 of 0.43, F = 34.70, and a r^2_{pred} of 0.46. The predicted activities of the dataset, along with R1 and R2 fragment contribution, are shown in Table **1**. Plots of the predicted *vs* actual (experimental) activity of the training set and the test set molecules are shown in **Figure 4**.

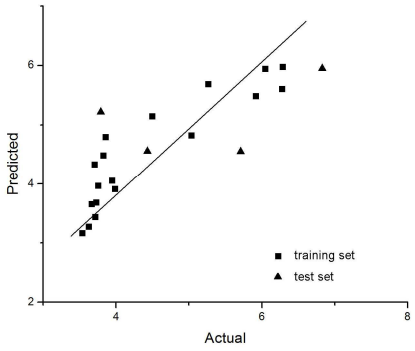


Figure 4. Graph of experimental versus predicted pEC50 values from topomer CoMFA.

The topomer CoMFA 3D contour maps around R1 and R2 (shown in **Figure 5**) were generated by plotting the coefficients from the model. Green polyhedra surrounded regions where more bulk is 'good' for increasing potency, while yellow polyhedra surrounded regions where less bulk is 'good'. Red and blue contours show regions of desirable negative and positive electrostatic interactions, respectively.

Yellow contours (**Figure 5a**) dominate the R1 group in the steric field and red contours (**Figure 5b**) occupy the electrostatic field; this suggests that small bulky groups with electronegative potential at the R1 site would be favorable for activity. Regarding the contours of the R2 group, yellow contours (**Figure 5c**) are located near R^2 and R^3; the red contours are located in the middle of the electrostatic field, and blue contours are located far away from the phenyl ring (**Figure 5d**); this demonstrates that a small bulky group with electronegative potential at the R2 site would improve the fungicidal activity.

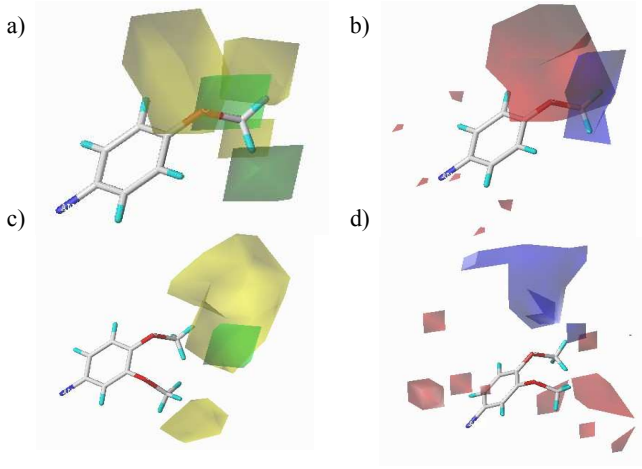


Figure 5. Contour maps of topomer CoMFA around R1 and R2. (a) Steric contour map for R1, (b) Electrostatic contour map for R1, (c) Steric contour map for R2, (d) Electrostatic contour map for R2.

Conclusions

We have designed and synthesized a series of substituted *N*-benzhydryl valinamide carbamate derivatives as potential cellulose synthase inhibitors. Subsequent evaluation of the fungicidal activities of these compounds revealed that the introduction of a dimethoxyphenyl group into the valinamide carbamate lead compound gave very good levels of fungicidal activity against *Phytophthora capsici* and *Pseudoperonospora cubensi*. The overall analyses (CoMFA and topomer CoMFA), suggests that the small bulky and electronegative nature of halobenzene (or methylbenzene) and dialkoxybenzene moieties are responsible for the higher potency of the molecules. Compounds **9e** and **9g** are particularly active against *Phytophthora capsic* and *Pseudoperonospora cubensi* and are also more potent than the control compound dimethomorph but less potent than mandipropamid. Further studies are currently underway in our laboratory to conduct field trials.

Experimental

Material and methods

^{1}H and ^{13}C NMR spectra were measured on a Bruker AC-P500 instrument using TMS as internal standard and $CDCl_3$ as 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. All

reagents are analytical grade.

Synthesis of (3,4-dimethoxyphenyl)(substituted phenyl)methanones (4a-4g).[22] To a suspension of substituted benzoic acid (54.28 mmol) in dry dichloromethane (60 mL), oxalyl chloride (108.57 mmol) and dimethylformamide (three drops) were added at room temperature. The crude mixture was refluxed for 2 h. It was concentrated *in vacuo*, washed with dichloromethane and concentrated again, twice. The substituted benzoyl chloride was isolated as a yellow oil in quantitative yield. This was transferred into a round-bottom flask and diluted with dichloromethane (50 mL). Aluminium trichloride (5.31 g, 39.81 mmol) was then added and the mixture was cooled to 0 °C. 1,2-Dimethoxybenzene (5.0 g, 36.19 mmol) was added dropwise and the mixture was refluxed for 2 h. The temperature was cooled to room temperature and the organic layer was washed with ice water (50 mL), 2 M HCl (20 mL), saturated aqueous sodium hydrogen carbonate (50 mL), dried over anhydrous sodium sulfate, and concentrated *in vacuo* to give compounds **4**.

General Synthetic Procedures for (3,4-dialkoxylphenyl)(substituted phenyl)methanols (3h-v).[23] To a suspension of magnesium shavings (0.59 g, 24.75 mmol) in anhydrous tetrahydrofuran (30 mL, nitrogen atmosphere) was added a small crystal of iodine. Substituted bromobenzene (22.5 mmol) was then added slowly (over 30 minutes), so as to maintain a gentle reflux. The mixture was heated to reflux for 3 h. After cooling to room temperature, the mixture was transferred to a pressure-equalizing dropping funnel with a syringe. To a solution of 3,4-dialkoxyl benzaldehyde (15 mmol) in anhydrous tetrahydrofuran (25 mL, nitrogen atmosphere) was added the solution of substituted-phenylmagnesium bromide slowly. After stirring at room temperature for 4 h, saturated ammonium chloride (30 mL) was added and the reaction was extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with brine (3 × 15 mL), dried over anhydrous sodium sulfate, and concentrated in vacuo to give compounds **3**.

Example data of **3i** is shown as follows, whereas data for the other compounds can be found in the Supporting Information.

Data for **3i**: white solid, yield = 93.0%, mp 95-96 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (dd, J = 8.4, 5.6 Hz, 2H, Ph-H), 7.02 (t, J = 8.7 Hz, 2H, Ph-H), 6.89 (s, 1H, Ph-H), 6.83 (s, 2H, Ph-H), 5.78 (s, 1H, Ph-H- Ph), 4.08 (q, J = 7.0 Hz, 2H, O$\underline{CH_2}CH_3$), 3.84 (s, 3H, O$\underline{CH_3}$), 1.45 (t, J = 7.0 Hz, 3H, OCH$_2\underline{CH_3}$). HRMS calcd for $C_{16}H_{17}FO_3$ ([M + Na]): 276.1054; Found: 276.1162.

General procedure for the synthesis of the (3,4-dialkoxylphenyl)(substituted phenyl)methanones (4h-v). 2-Iodoxybenzoic acid (IBX) (15 mmol) was added to a solution of (3,4-dialkoxylphenyl)(substituted phenyl)methanol **3** (10 mmol) in dimethylsulfoxide (25 mL), and the resulting mixture was stirred at room temperature for 4 h. Water (100 mL) was then added, and the resulting mixture was extracted with diethyl ether (4 × 20 mL). The combined organic layers were washed with brine (6 × 20 mL), dried over anhydrous sodium sulfate, and concentrated *in vacuo* to give compounds **4**.

Example data of **4i** is shown as follows, whereas data for the other compounds can be found in the Supporting Information.

Data for 4i: white solid, yield = 94.5%, mp 92-94 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (dd, J = 8.4, 5.6 Hz, 2H, Ph-H), 7.46 (d, J = 1.5 Hz, 1H, Ph-H), 7.32 (dd, J = 8.3, 1.6 Hz, 1H, Ph-H), 7.15 (t, J = 8.5 Hz, 2H, Ph-H), 6.88 (d, J = 8.4 Hz, 1H, Ph-H), 4.19 (q, J = 7.0 Hz, 2H, O$\underline{CH_2}CH_3$), 3.93 (s, 3H, O$\underline{CH_3}$), 1.52 (t, J = 7.0 Hz, 3H, OCH$_2\underline{CH_3}$). HRMS calcd for $C_{16}H_{15}FO_3$ ([M + H]): 274.1084; Found: 274.1005.

General procedure for the synthesis of the (3,4-dialkoxylphenyl)(substituted phenyl)methanone oximes (5a-v) Sodium hydroxide (1.20 g, 30 mmol) was added in a single portion to a solution of (3,4-dialkoxylphenyl)(substituted phenyl)methanone **4** (20 mmol) and hydroxylamine hydrochloride (2.07 g, 30 mmol) in anhydrous ethanol (50 mL), and the resulting mixture was heated at reflux for 6 h. The reaction was then cooled to room temperature and concentrated *in vacuo* to give a residue, which was extracted with dichloromethane (3 × 50 mL), and the combined organic layers were washed with water (3 × 15 mL), dried over anhydrous sodium sulfate, and concentrated *in vacuo* to give compounds **5**.

Example data of **5k** is shown as follows, whereas data for the other compounds can be found in the Supporting Information.

Data for **5k**: white solid, yield = 81.7%. mp 87 - 89℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (ddd, J = 25.4, 22.1, 4.9 Hz, 4H, Ph-H), 7.14 (d, J = 8.0 Hz, 1H, Ph-H), 6.96 (dd, J = 12.0, 10.3 Hz, 1H, Ph-H), 6.80 (dt, J = 21.7, 5.2 Hz, 1H, Ph-H), 4.13 (dd, J = 22.3, 7.0 Hz, 2H, O$\underline{CH_2}CH_3$), 3.84 (d, J = 5.6 Hz, 3H, O$\underline{CH_3}$), 2.41 (s, 1H), 1.51 – 1.45 (m, 3H, OCH$_2\underline{CH_3}$). HRMS calcd for $C_{17}H_{19}NO_3$ ([M + H]): 285.1442; Found: 285.1365.

General procedure for the synthesis of the (3,4-dialkoxylphenyl)(substituted phenyl)methanamines (6a-v) A solution of 28% (w/w) aqueous ammonia (70 mL) was added to a suspension of (3,4-dialkoxylphenyl)(substituted phenyl)methanone oxime (23.11 mmol), zinc powder (7.51 g, 115.56 mmol) and ammonium acetate (1.78 g, 23.11 mmol) in ethanol (140 mL) and the resulting mixture was heated at reflux for 1 h. The mixture was then cooled to room temperature and filtered to remove the zinc. The filtrate was collected and the organic solvent removed *in vacuo* to give a residue, which was extracted with ethyl acetate (4 × 50 mL). The combined organics were then washed sequentially with saturated aqueous sodium hydrogen carbonate (50 mL) and brine (3 × 50 mL) before being dried over anhydrous sodium sulfate and concentrated *in vacuo* to give compounds **6**.

Example data of **6i** is shown as follows, whereas data for the other compounds can be found in the Supporting Information.

Data for **6i**: yellow oil (4.63 g). yield = 77.9%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.28 (m, 2H, Ph-H), 6.98 (t, J = 8.4 Hz, 2H, Ph-H), 6.93 – 6.74 (m, 3H, Ph-H), 5.14 (s, 1H, $\underline{CH}$NH), 4.06 (dd, J = 13.6, 6.7 Hz, 2H, O$\underline{CH_2}CH_3$), 3.83 (s, 3H, O$\underline{CH_3}$), 1.44 (t, J = 6.8 Hz, 3H, OCH$_2\underline{CH_3}$). HRMS calcd for $C_{16}H_{18}FNO_2$ ([M + H]): 275.1137; Found: 275.1322.

Synthesis of (S)-2-((isopropoxycarbonyl)amino)-3-methylbutanoic acid

(8).[24] L-Valine **7** (0.3 mol) and isopropyl chlorocarbonate (0.36 mol) were added sequentially in a drop-wise manner to a stirred solution of sodium hydroxide (0.6 mol) in water (300 mL) at 0 °C, and the resulting mixture was stirred at room temperature for 1 h. The reaction mixture was then washed with ethyl acetate (100 mL) before being acidified with 2 M HCl to pH 2-3 and extracted with ethyl acetate (4 × 50 mL). The combined extracts were dried over anhydrous sodium sulfate and concentrated *in vacuo* to give compound **8** as a white solid (mp: 70–72 °C, Yield = 91.0%).

General Procedure for the synthesis of the isopropyl ((2S)-1-(((3,4-dialkoxylphenyl) (substituted phenyl)methyl)amino)-3-methyl-1-oxobutan-2-yl)carbamates (9a-v). Triethylamine (6 mmol) was added to a solution of (S)-2-((isopropoxycarbonyl)amino)-3-methylbutanoic acid **8** (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 ((3,4-dialkoxyl phenyl)(substituted phenyl)methanamine **6** (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 2 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 compounds **9**.

Example data of **9h** is shown as follows, whereas data for the other compounds can be found in the Supporting Information.

Data for **9h**: white solid, yield = 94.1%. mp 142 – 144 °C.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.24 (m, 3H, Ph-H), 7.21 (d, J = 7.1 Hz, 2H, Ph-H), 6.77 (dd, J = 11.6, 8.6 Hz, 2H, Ph-H), 6.69 (d, J = 5.8 Hz, 1H, Ph-H), 6.17 (d, J = 7.6 Hz, 1H, CHNHCO), 5.17 (d, J = 7.7 Hz, 1H, Ph-CHNH), 4.85 (d, J = 6.3 Hz, 1H, Ph-CH-Ph), 4.14 – 4.03 (m, 2H, CH_3CH_2O), 4.02 – 3.92 (m, 1H, COCHNH), 3.79 (s, 3H, OCH_3), 3.21 – 2.92 (m, 1H, $(CH_3)_2CHO$), 2.15 (m, 1H, $(CH_3)_2CHCH$), 1.44 (t, J = 7.0 Hz, 3H, CH_3CH_2O), 1.20 (dd, J = 12.7, 6.6 Hz, 6H, $(CH_3)_2CHO$), 0.93 (dd, J = 17.8, 6.3 Hz, 6H, $(CH_3)_2CHCH$). HRMS calcd for $C_{25}H_{34}N_2O_5$ ([M + H]): 442.2540; Found: 442.2468.

Fungicidal Activities

Fungicidal activity against *Phytophthora capsici* (*in vitro*). The *in vitro* fungicidal activities of the synthesized compounds against *Phytophthora capsici* were determined as previously described.[25-27] The results are summarized in Table 1.

Fungicidal activity against *Phytophthora capsici* (*in vivo*).[28] Plants infected with *P. capsici* were collected from pepper fields in Tianjin, China, in 2012. The pathogenic fungal isolates of *P. capsici* were grown on V8 juice agar medium at room temperature for 7 days.[29] To simulate the formation of sporangium, the cultures were maintained under light at 24 °C for seven days. When abundant sporangia had formed, the sterile solution was replaced with sterile distilled water and the plates were maintained at 4 °C for 30 min and then left at room temperature (20–24 °C) for 1 h to enhance the release of zoospores from the sporangia. The flooding water, which contained zoospores and mycelium, was filtered using two layers of cheesecloth, and the concentration of the zoospore suspension was subsequently adjusted to approximately 1 × 10^6 zoospores mL^{-1} using a hemocytometer. The inoculum was then used immediately.

The inoculation tests were conducted under greenhouse and growth chamber conditions. The pepper plants (*Capsicum annuum* L.) were grown in plastic trays (50 × 30 × 5 cm) in a greenhouse at 25 ± 2 °C in a sterilized mixture of vermiculite and worm cast (5:1 - v/v). The commercial fungicide dimethomorph was used as a positive control to compare its antifungal activity with those of the synthesized compounds **9**. The title compounds **9** and dimethomorph were dissolved separately in DMF, and the resulting solutions were diluted to give concentrations of 6.25, 12.5, 25, 50.0 and 100 μg mL^{-1}. When the plants had six leaves, each pepper root was treated with 1 mL of a solution of each chemical by making 1 cm long incisions in the pepper plant 1 day prior to the inoculation with *P. capsici*. The zoospore inoculation of the pepper roots was performed by inoculating 1 mL of zoospore inoculum of *P. capsici* according to the same procedure used for the chemical treatment process. Six seedlings at the four-leaf stage were transplanted into a plastic pot (5 × 30 × 5 cm) containing the soil mix described previously. Seedlings that had been drenched with sterile distilled water instead of the zoospore inoculum were used as a negative control. Disease severity was evaluated after 7 days using a 0–5 scale (0 = no visible disease symptoms; 1 = leaves slightly wilted with brownish lesions beginning to appear on their stems; 2 = 30–50% of the entire plant diseased; 3 = 50–70% of the entire plant diseased; 4=70–90% of the entire plant diseased; 5 = dead plant). The results are listed in **Table 2**.

Fungicidal activity against *Pseudoperonospora cubensi* (*in vivo*).[30] Cucumber plants, which were cultivated by Shandong Mici with one fully expanded true leaf, were maintained in a greenhouse. The commercial fungicide dimethomorph was used as a positive control and its antifungal activity compared with those of the synthesized compounds **9**. The synthesized compounds **9** and dimethomorph dissolved separately in DMF, and the resulting solutions were diluted to give the concentrations of 12.5, 25, 50.0, 100 and 200 μg mL^{-1}. The plants were then sprayed with these different fungicide solutions and allowed to dry in air for approximately 2 h. Cultures of *P. cubensis* were maintained on the cucumber plants and the spores were collected by shaking the leaves in water. The lower surfaces of the treated cucumber leaves were then sprayed with a spore suspension of ca 100 000 spores mL^{-1}. The plants were transferred to a thermo-hygrostat and held at 20 °C and >90% humidity for 5 days to allow for infection. The plants were then held in the greenhouse for 5 more days before being examined for their disease control score. The results are listed in Table 2.

Topomer CoMFA and Prediction of the Inhibitory Activity.

The Topomer CoMFA program in the SYBYL-X software package was used to perform all calculations. A 3D-QSAR model was generated by splitting the molecules into fragments, topomerically aligning each fragment, and calculating steric

and electrostatic field descriptor values for the topomerically aligned fragments to create a CoMFA table with the field descriptor values. All molecules of the dataset were separated into two fragments shown as R1 and R2 groups as shown in **Figure 3**. Template molecules **9g** were chosen for fragmentation. Each topomer fragment was applied with topomer alignment to make a 3D invariant representation. Steric and electrostatic interaction energies were calculated using the carbon sp^3 probe.

All the models were investigated using the full cross-validated r^2 (q^2) PLS leave-one-out (LOO) method with CoMFA standard options for scaling of the variables. A progressive scrambling method was applied to determine the sensitivity of QSAR models to chance correlations.

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