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Design, synthesis, and fungicidal activities of imino diacid analogs of valine amide fungicides

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ABSTRACT

The novel imino diacid analogs of valine amides were synthesized via several steps, including the protection, amidation, deprotection, and amino alkylation of valine, with the resulting structures confirmed by ^{1}H and ^{13}C NMR and HRMS. Bioassays showed that some of these compounds exhibited good fungicidal activity. Notably, isopropyl 2-((1-((1-(3-fluorophenyl)ethyl)amino)-3-methyl-1-oxobutan-2-yl)amino) propanoate **5i** displayed significant levels of control, at 50%, against *Erysiphe graminis* at 3.9 μM as well as a level of potency very similar to the reference azoxystrobin, which gave 60% activity at this concentration. The present work demonstrates that imino diacid analogs of valine amides could be potentially useful key compounds for the development of novel fungicides against wheat powdery mildew.

Environmental problems caused by traditional pesticides, because of their nonbiodegradable properties and residues in soil, water resources, and crops, have been a concern for both scientists and the public in recent years.[1] Results from studies of environmental friendly and biodegradable pesticides can be used to reduce environmental problems while maintaining crop yields. Amino acids play central roles both as building blocks of peptides and proteins and as important constituents of biologically active compounds, such as drugs and agrochemicals.[2] They are also an excellent alternative to synthetic pesticides as a means for reducing negative chemical impacts on human health and the environment. Peptide drugs have also been successfully applied in treating certain human diseases. Currently, peptide/protein drugs constitute more than 10% of the ethical drug market.[3] However, only a few amino-acid-containing pesticides have progressed through development for marketing as commercial products. Glyphosate is the most important and famous amino-acid-containing pesticide. Iprovalicarb is a member of the valinamide carbamate fungicides[4], which are one of three subclasses of carboxylic acid amide (CAA) fungicides.[5] In 1998, iprovalicarb was the first commercial amino-acid-containing fungicide to be introduced. Until now, three valinamide carbamates, including benthiavalicarb,[6] iprovalicarb, and valiphenal,[7] have been commercialized for the control of oomycete diseases (Fig. 1).

Oomycetes can cause several destructive diseases in a range of important crop plants, such as late blight on potatoes, blue mold on tobacco, and grape downy mildew.[5] Valinamide carbamate fungicides exhibit high activity against most foliar oomycete plant pathogens, such as *Plasmopara viticola* in grapes, *Phytophthora infestans* in potatoes and tomatoes, and *Pseudoperonospora cubensis* in cucurbits.

In our previous study, we reported the synthesis and evaluation of the fungicidal activities of a series of CAA derivatives. *N*-Benzhydryl valinamide carbamate derivatives exhibited excellent fungicidal activity in vitro against *Phytophthora capsici* and *Pseudoperonospora cubensis*.[8] However, this carbamate might be too easily naturally degraded. And it was also reported that two atom spacer in the field of mandelamides (CAA fungicides) gave excellent fungicidal results.[9] With this in mind, a series of dipeptidomimetics, imino diacid analogs of valine amides, was designed by adding methylene groups between the carbamate nitrogen atom and carbonyl group to find novel compounds with high fungicidal activities (Fig. 2).

Herein, a series of novel imino diacid analogs of valine amide fungicides was synthesized and their fungicidal activities were evaluated. The results revealed that these compounds displayed promising fungicidal activity against wheat powdery mildew but not against oomycete plant pathogens. This means that these compounds might have different mechanism of fungicide action from CAA fungicides. As powdery mildew is a serious fungal disease that affects a wide range of plants, causing yield losses up to 45 percent, the potential for application of the present compounds against this disease is encouraging.

Compounds **5a**–**o** and **6a**–**o** were synthesized as shown in Scheme 1. Imino diacid analogs of valine amides were synthesized

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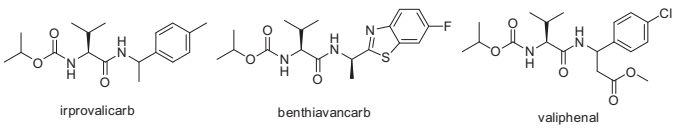


Figure 1. Structures of commercial valinamide carbamate fungicides.

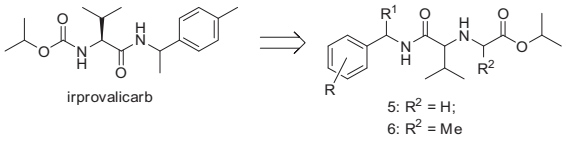
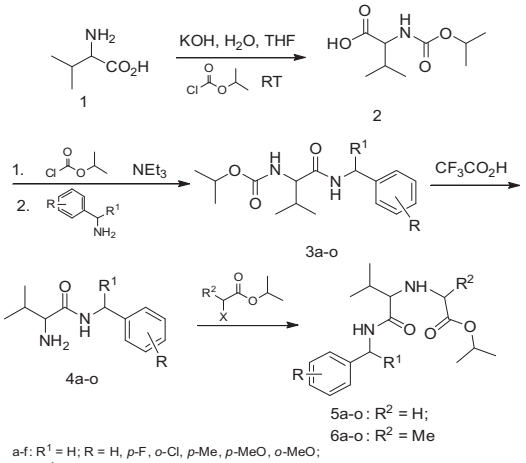


Figure 2. Design of the target compounds.



Scheme 1. The synthetic route to compounds **5a**–**o** and **6a**–**o**.

by preparing *N*-protected valine **2** starting from valine **1** and isopropyl chloroformate in dry THF and KOH solution. Isopropyloxycarbonyl-L-valine **2** was treated with isopropyl chloroformate under basic conditions in THF to yield the mixed anhydride (not isolated), which was then treated with triethylamine and corresponding amines in THF, which yielded *N*-protected valinamides **3a**–**o**. After trifluoroacetic acid deprotection, the free amino group of the deprotected valinamides **4a**–**o** could react with isopropyl chloroacetate or 2-bromopropionate to form imino diacid analogs of valine amides, **5a**–**o** or **6a**–**o** (see Supplementary).

The newly synthesized compounds, acetate derivatives **5a**–**o** and propanoate derivatives **6a–o**, were evaluated for their antiviral activity against *P. capsici* and *E. graminis*. Interestingly, these compounds proved ineffective against *P. capsici*, which are oomycete plant pathogens, but effective against *E. graminis*, an ascomycotina plant pathogen. This indicated that these compounds might possess a novel mechanism of action. Results regarding these compounds' fungicidal effects against *E. graminis* showed that most of these compounds were ineffective against *E. graminis*, but some of them exhibited excellent fungicidal activity (Table 1). Under equivalent dosage conditions of 1000 μM, compounds **5b** and **6a** displayed significant levels of control at 100% and 60% against *E. graminis*, respectively, whereas compounds **5f**, **5i**, **5j**, **5k**, **6d**, and **6o** showed 100% inhibition. The activities of these compounds against *E. graminis* were therefore measured using dose reduction at serial four-fold dilutions. Under equivalent dosage conditions of 250 μM, fungicidal activity by compounds **5b** and **5f** disappeared completely. The activity of compounds **5j**, **5k**, **6d**, and **6o** decreased to 90%, 80%, 90% and 90%, respectively, whereas compound **5i** still showed 100% inhibition at these lower concentrations. When the concentration was further reduced to 15.6 μM, compounds **5i**, **5j**, **5k**, and **6o** displayed good levels of control of 100%, 60%, 70%, and 50% against *E. graminis*, respectively. Compound **5i** still displayed good levels of control, at 50%, with 3.9 μM, and a level of potency very similar to that of azoxystrobin (60%). Clearly, the acetate derivatives **5** exhibited higher fungicidal activity than propanoate derivatives **6**, and derivatives of **5** with the substituent group in the *meta* position, showed higher fungicidal activity than derivatives of **5** with *para* or *ortho*-position substituent groups. Introduction of fluorine atoms into the *meta* position of the phenyl group significantly enhanced their fungicidal activity.

Table 1
Fungicidal Activity of the Compounds against *Erysiphe graminis*

No.	R	R^1	R^2	Fungicidal activity (%) at concd (μM)				
				1000	250	62.5	15.6	3.9
5a	H	H	H	0	—	—	—	—
5b	*p*-F	H	H	100	0	—	—	—
5c	*o*-Cl	H	H	0	—	—	—	—
5d	*p*-Me	H	H	0	—	—	—	—
5e	*p*-MeO	H	H	0	—	—	—	—
5f	*o*-MeO	H	H	100	0	—	—	—
5g	H	Me	H	0	—	—	—	—
5h	*p*-F	Me	H	0	—	—	—	—
5i	*m*-F	Me	H	100	100	100	100	50
5j	*p*-Me	Me	H	100	90	80	60	—
5k	*p*-CF_3	Me	H	100	80	80	70	—
5l	*p*-MeO	Me	H	0	—	—	—	—
5m	*m*-MeO	Me	H	0	—	—	—	—
5n	*p*-EtO	Me	H	0	—	—	—	—
5o	3,4-DiMe	Me	H	0	—	—	—	—
6a	H	H	Me	60	—	—	—	—
6b	*p*-F	H	Me	0	—	—	—	—
6c	*o*-Cl	H	Me	0	—	—	—	—
6d	*p*-Me	H	Me	100	90	20	0	—
6e	*p*-MeO	H	Me	0	—	—	—	—
6f	*o*-MeO	H	Me	0	—	—	—	—
6g	H	Me	Me	0	—	—	—	—
6h	*p*-F	Me	Me	0	—	—	—	—
6i	*m*-F	Me	Me	0	—	—	—	—
6i	*p*-Me	Me	Me	0	—	—	—	—
6k	*p*-CF_3	Me	Me	0	—	—	—	—
6l	*p*-MeO	Me	Me	0	—	—	—	—
6m	*m*-MeO	Me	Me	0	—	—	—	—
6n	*p*-EtO	Me	Me	0	—	—	—	—
6o	3,4-DiMe	Me	Me	100	90	80	50	—
	Azoxystrobin			100	100	100	100	60

*No test.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2015.10.089.

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