Bioorganic & Medicinal Chemistry xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Synthesis and anti-oomycete activity of novel quinazolin- and benzothiazol-6-yloxyacetamides: Potent aza-analogs and five-ring analogs of quinoline fungicides

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ARTICLE INFO

Article history:
Received 30 June 2015
Revised 30 July 2015
Accepted 12 August 2015
Available online xxxx

Keywords:
Quinazoline
Benzothiazole
Heterocycle
Fungicide
Crop protection

ABSTRACT

Novel quinazolin- and benzothiazol-6-yloxyacetamides show excellent in vivo activity against the three economically most important Oomycete pathogens *Phytophthora infestans*, *Plasmopara viticola* and *Pythium ultimum*. They are polar analogs of known quinolin-6-yloxyacetamides, which are not active against the soil-borne damping-off disease caused by *Pythium ultimum*. The Bogert quinazoline synthesis, an almost forgotten heterocyclization technique, proved to be highly useful for the concise construction of required quinazolin-6-ol building blocks.

1. Introduction

Recently we have published the synthesis and structure–activity relationship of quinolin-6-yloxyacetamides.[1] The members of this novel class of experimental fungicides exhibited excellent control of a whole range of phytopathogens from the group of Ascomycetes and Oomycetes. Their fungicidal activity is due to their ability to inhibit the fungal tubulin polymerization, leading to microtubule destabilization. In our continued search for new fungicides with potent anti-oomycete activity[2] we have found, that analogs in which the pyridine moiety of quinolin-6-yloxyacetamides such as **1** has been replaced by a pyrimidine (→**2**) or a thiazole ring (→**3**), show excellent activity against the three economically most important Oomycete diseases. These include the foliar diseases potato late blight (caused by *Phytophthora infestans*) and grape downy mildew (resulting from *Plasmopara viticola* as causal agent) as well as the soil-borne damping-off disease of several different crops (for which *Pythium ultimum* is responsible). As there are numerous examples known in which replacement of ring carbon atoms by heteroatoms can lead to improved water solubility,[3–8] it does not come by surprise that increasing the number of heteroatoms in our bicyclic scaffold results in higher efficacy against the later pathogen, Pythium ultimum, because of enhanced systemicity which seems to be required for the efficient control of this soil-borne disease. In this paper we summarize the results of our investigation of synthesis, phys–chem properties and structure–activity relationships of novel quinazolin-6-yloxyacetamides, such as **2**, and 1,3-benzothiazol-6-yloxyacetamides, such as **3** as potent aza-analogs or five-ring analogs of quinolin-6-yloxyacetamide fungicides, such as **1** (Fig. 1).

2. Results and discussion

2.1. Synthesis

2.1.1. Quinazolines

The trisubstituted heterobicyclic scaffold of the lead structure **1** had been prepared by a Skraup-type quinoline synthesis,[9] which is not applicable to the quinazoline core, therefore we had to look for a different approach. For the synthesis of the 8-unsubstituted quinazolines, such as **2**, we decided to apply Bogert's quinazoline synthesis[10–12] as it allowed us to obtain the required intermediate 6-hydroxyquinazoline (**7**) from inexpensive 3-hydroxybenzaldehyde (**4**) (Scheme 1). This quinazoline synthesis, which is not found very often in the literature,[12] starts with the regioselective nitration to deliver **5**. This disubstituted benzaldehyde is then converted with formamide under a hydrogen chloride gas stream

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http://dx.doi.org/10.1016/j.bmc.2015.08.009
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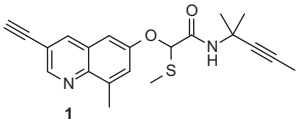
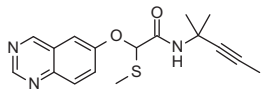
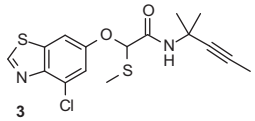


1
typical example of quinolin-6-yloxy-acetamide lead compounds



2
quinazolin-6-yloxyacetamide analog



3
benzothiazol-6-yloxyacetamide analog

Figure 1. Fungicidally active quinazolin- and benzothiazol-6-yloxyacetamides **2** and **3** and their lead structure **1**.

into the *N*,*N*′-diformylated aminal **6**, which undergoes reductive cyclization by treatment with zinc in acetic acid to deliver directly the desired building block **7**. Its hydroxyl function can be easily alkylated with α-halocarboxylates leading to the quinazolin-6-yloxyacetamides **8** and **10** bearing either an ethyl or a thiomethyl group at the α-carbon atom of the ester. These two functionalities played already the biggest role during the optimization of the quinolin-6-yloxyacetamide lead compounds, such as **1**.[1] It is noteworthy that this alkylation reaction introduces completely different functional groups under the same reaction conditions, as the hydroxyl function of **7** has been transformed into an ether (→**8**) as well as into a *O*,*S*-acetal (→**10**). The saponification of the ester function in **8** and **10** to the corresponding carboxylic acids and their further conversion with 1,1-dimethylpropargylamine and 1,1-dimethyl-2-butynylamine, respectively, under peptide coupling conditions finally led to the fungicidally active amides **2** and **9**.

One of the results of the structure–activity relationship study of the quinoline lead compound class was that small lipophilic substituents in ring position 8 often have a positive impact on the fungicidal activity.[1] In this regard halogens atoms and the methyl group were of particular interest. As the disubstituted anthranilic acid **12** was available in larger amounts, we decided to approach 8-methylquinazolin-6-yloxyacetamides such as **22** via a Niementowski synthesis.[13,14] First we had to transfer 3-methyl-5-iodoanthranilic acid (**12**) via esterification to **13**, amine protection to **14**, methoxylation to **15** and deprotection to the disubstituted methyl anthranilate **16**. Under the conditions of Leonard's variation[15] of the Niementowski quinazoline synthesis, which uses an amidine as coupling partner instead of the Niementowski-typical amide, the quinazolinone **17** was formed. Three further manipulations, the chlorination to **18**, subsequent reduction and ether cleavage delivered the desired 6-hydroxy-8-methyl-6-hydroxyquinazoline **19**. The finalization of the synthesis is achieved by using the same last three steps as already applied for the preparation of **2** in Scheme 1, which are alkylation of the phenol function to **20**, ester saponification to **21** and amide coupling, delivering **22**, the 8-methylated analog of **2** (Scheme 2).

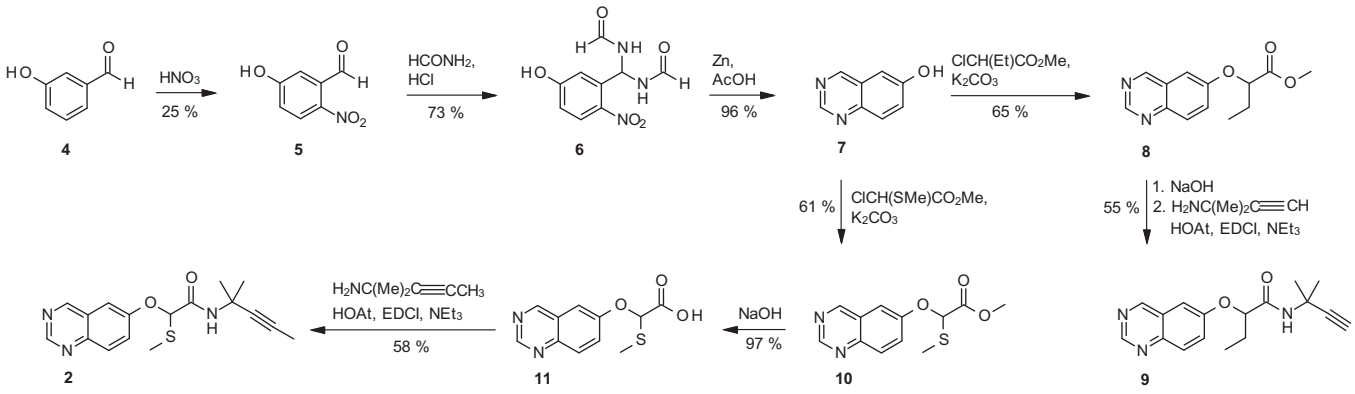
2.1.2. Benzothiazoles

For the synthesis of 4-chlorobenzothiazol-6-yloxyacetamides, such as **3**, we chose 2-chloro-4-methoxyaniline (**23**) as starting material, which could be cyclized to the 2-aminobenzothiazole derivative **24** upon treatment with potassium thiocyanate and bromine. This standard 2-aminobenzothiazole synthesis proceeds via an *ortho*-thiocyanato-aniline intermediate, which undergoes ring closure by reaction with bromine.[16–18] For the following deamination we applied Chedekel's conditions[19,20] with sodium nitrite and phosphinic acid. The ether cleavage of the resulting methoxy-substituted benzothiazole **25** delivered the desired 4-chloro-6-hydroxybenzothiazole **26**. Again the same last three steps as in Schemes 1 and 2, alkylation with an α-chlorocarboxylate to **27**, ester saponification to **28** and finally amidation afforded the benzothiazol-6-yloxyacetamide **3** (Scheme 3).

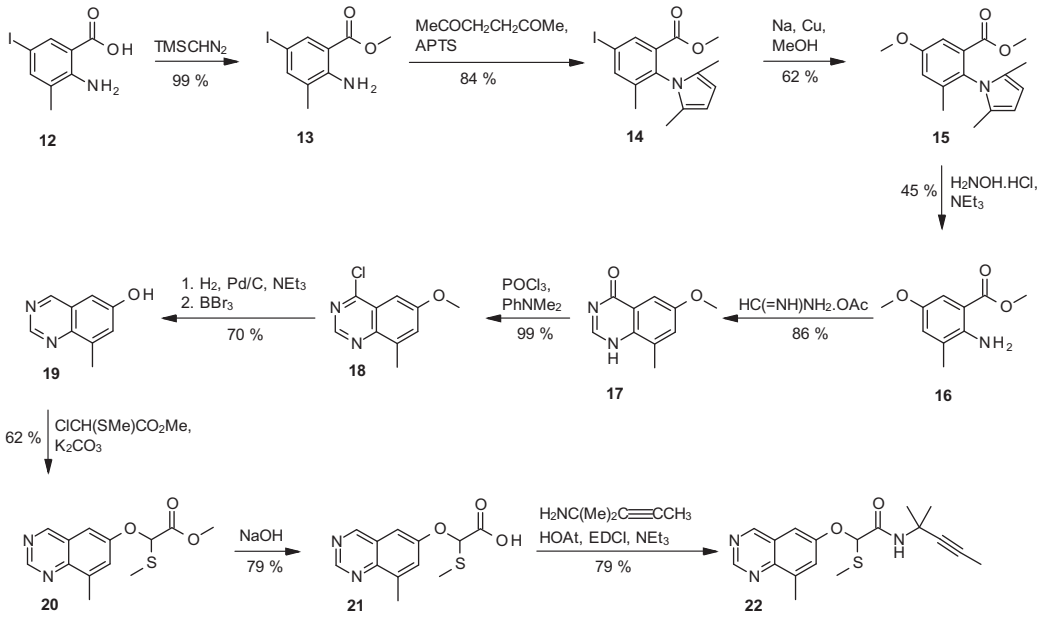
2.2. Structure–activity relationship

2.2.1. Influence of the physico-chemical properties on the Pythium activity

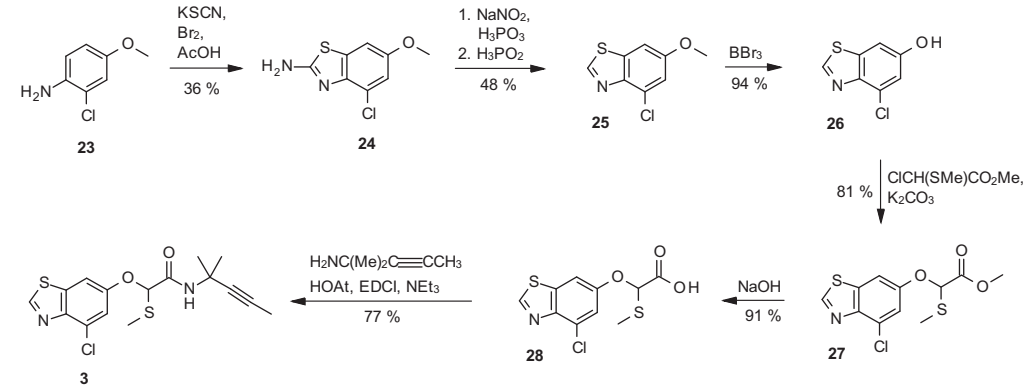
Some of the quinoline lead compounds, such as **1**, showed useful activity against the foliar Oomycete diseases *Phytophthora infestans* and *Plasmopara viticola*. However, their strength was clearly powerful efficacy against plant pathogens from the Ascomycetes genus, especially leaf spot diseases such as wheat leaf blotch caused by *Mycosphaerella graminicola* and barley net blotch with *Pyrenophora teres* as causal agent.[1] This is in stark contrast to the fact that good in vivo activity against the soil-borne Oomycete pathogen *Pythium ultimum* was never observed with quinolin-6-yloxyacetamides. A major reason for this spectrum gap is probably their lipophilicity, as a requirement for efficient Pythium control is a certain degree of systemicity, driven by low log*P* and high water solubility values. Because we had been looking for a solution against all three economically Oomycete pathogens *Phytophthora infestans*, *Plasmopara viticola* and *Pythium ultimum*, we decided to design close analogs of the fungicidally active quinolin-6-yloxyacetamides with improved physico-chemical properties. Table 1 compares the Pythium activity, log*P* values and water solubility of four different compounds, which are all linked via the same *O*, *S*-acetal to the same N-alkynylated amide. Although the two quinoline derivatives (entries 1 and 2) bearing iodo and ethynyl



Scheme 1. Synthesis of the fungicidally active quinazolin-6-yloxyacetamides **2** and **9**.



Scheme 2. Synthesis of the fungicidally active quinazolin-6-yloxy acetamide **22**.



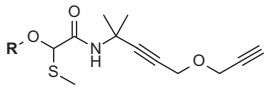
Scheme 3. Synthesis of the fungicidally active benzothiazol-6-yloxyacetamide **3**.

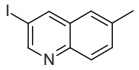
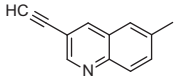
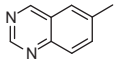
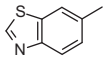
groups were two of the best possible substituents in position 3 against Ascomycetes species,[1] they are inactive in our standard in vivo Pythium assay and also in the in vitro Pythium test. Table 1 shows that they are certainly weaker than the corresponding quinazoline and benzothiazole derivatives (entries 3 and 4). This clearly correlates with the higher polarity of the quinazoline and the benzothiazole, demonstrated by the lower log*P* value and the much higher water solubility compared to the similar quinolines.

2.2.2. Influence of the substitution pattern on the anti-oomycete activity

After we had confirmed the superiority of quinazolines and benzothiazoles in the control of Pythium compared to corresponding quinoline derivatives, we wanted to check their potency against the two other Oomycete diseases *Phytophthora infestans* and *Plasmopara viticola*. Furthermore we wanted to acquire information about the influence of different substituents on the fungicidal activity. Based on the structure–activity relationship experience with the quinolin-6-yloxyacetamides,[1] we focused mainly on unsubstituted quinazolines as well as on benzothiazoles and quinazolines with a methyl group in position 8 and on benzothiazoles with a methyl or chloro substituent in positions 2 or 4. In addition the impact of replacing the acetamide linker with a thiomethyl or ethyl substituent was investigated. The in vivo results for the whole set of compounds with the same dimethylbutynylamine moiety against the three mentioned Oomycete diseases are summarized in Table 2. The mentioned values show the activity at rather low use rates, for *Phytophthora infestans* and *Plasmopara viticola* at 60 ppm (corresponding to only 60 g/ha), for *Pythium ultimum* at 20 ppm. As a general trend, the benzothiazole derivatives appear to be stronger than the corresponding quinazoline derivatives, Another trend is that compounds with an ethyl group in the acetamide linker (entries 3 and 9) are clearly weaker than their counterparts with a thiomethyl group in the same position (entries 1 and 4). Whereas a methyl or chloro substituent in quinazoline position 8 and benzothiazole position 4 seems to deliver a better overall activity across all three pathogens (entries 2, 6 and 7), remarkably, a chloro or methyl substituent at the ring carbon between both benzothiazole heteroatoms (position 2) completely destroys the activity (entries 5 and 10). Another notable manipulation which leads to full loss of activity is the oxidation of the thiomethyl group in the acetamide linker to a sulfoxide function (entry 8) (Table 2).

Table 1
Influence of the physico-chemical properties on the Pythium activity[a]



Entry	R	*Pythium ultimum* (damping-off disease) Liquid culture (in vitro)	*Pythium ultimum* (damping-off disease) Pouch (in vivo)	Log*P*	Water solubility (ppm)
1		20	0	3.99	2.5
2		70	0	3.45	12
3		80	70	1.92	1139
4		100	50	2.52	211

[a] Results are given in % activity at 6 ppm for the in vitro assay and at 20 ppm for the in vivo assay against *Pythium ultimum*.

3. Conclusions

The introduction of an additional heteroatom into the heterobicyclic core of quinolin-6-yloxyacetamides opens new avenues for the control of foliar and soil-borne Oomycete diseases, as the resulting quinazoline and benzothiazole analogs offer in addition to good activity against *Phytophthora infestans* and *Plasmopara viticola* also in vivo potency against *Pythium ultimum*. Their improved physico-chemical properties seem to play a key role in favouring this latter activity. Simple benzaldehydes, such as **4**, and anilines, such as **23**, can be employed as starting materials for the synthesis of the hydroxylated quinazoline and benzothiazole building blocks **7** and **26**. For this purpose the Bogert quinazoline synthesis,[10–12] a relatively underutilized heterocyclization reaction, seems to offer greater practicality than the more well-known Niementowski quinazoline synthesis, because it starts from anilines, which are usually abundantly available, instead of anthranilic acids. The last three steps of the reaction sequence to **2** and **3** (alkylation of phenol, ester saponification and amidation) are in analogy to the already described quinolin-6-yloxyacetamides.

In summary, a structure–activity relationship study revealed similarities of the novel quinazolin- and benzothiazol-6-yloxyacetamides to the related quinoline derivatives. Compounds with a thiomethyl substituent at the α-carbon atom of the acetic acid moiety are more active than the corresponding ethyl-substituted analogs. Quinazolines and benzothiazoles with a methyl or halogen substituent in positions 8 and 4, respectively, show better activity against all three important Oomycete diseases than the comparable unsubstituted analogs. Especially notable is the 4-methyl analog of **3** (entry 7 of Table 2) which delivers very strong in vivo activity against all three Oomycete diseases at low application rates.

4. Experimental section

4.1. Chemistry

All new compounds were characterized by standard spectroscopical methods. ^{1}H NMR spectra were recorded on a Varian Unity 400 spectrometer at 400 MHz using $CDCl_3$ as solvent and tetramethylsilane as internal standard. Chemical shifts are reported in ppm downfield from the standard (δ = 0.00), coupling constants in Hz. LC–MS spectra were determined using the following apparatus: ACQUITY UPLC from Waters, Phenomenex Gemini C18, 3 mm particle size, 110 Angström, 30 × 3 mm column, 1.7 mL/min, 60 °C, H_2O + 0.05% HCOOH (95%)/CH_3CN/MeOH 4:1 + 0.04% HCOOH (5%)—2 min—CH_3CN/MeOH 4:1 + 0.04% HCOOH (5%)—0.8 min; ACQUITY SQD Mass Spectrometer from Waters, ionization method: electrospray (ESI), Polarity: positive ions, Capillary (kV) 3.00, Cone (V) 20.00, Extractor (V) 3.00, Source Temperature (°C) 150, Desolvation Temperature (°C) 400, Cone Gas Flow (L/Hr) 60, Desolvation Gas Flow (L/Hr) 700. Analytical thin-layer chromatography (TLC) was performed using silica gel 60 F524 precoated plates. Preparative flash chromatography was performed using silica gel 60 (40–63 μm, E. Merck). Unless otherwise stated, all reactions were carried out under anhydrous conditions in an inert atmosphere (nitrogen or argon) with dry solvents.

4.1.1. 5-Hydroxy-2-nitrobenzaldehyde (5)

3-Hydroxybenzaldehyde (21 g, 0.17 mol) were slowly added to 200 ml of 28% nitric acid. Subsequently the mixture was neutralized with aqueous sodium hydroxide solution and stirred for 1 h at room temperature. The resulting yellow precipitate was filtered and then dissolved in 150 ml of benzene. This mixture was heated to reflux for 30 min and then cooled down to room temperature. The insoluble material was recovered by filtration and recrystallized from water to deliver (**5**, 7.0 g, 42 mmol, 25%) as yellow crystals. Mp, 167–168 °C. ^{1}H NMR ($CDCl_3$): δ = 6.16 (br s, 1H), 7.13 (dd, 1H), 7.29 (d, 1H), 8.16 (d, 1H), 10.48 (s, 1H). LC–MS: Rt = 1.33 min; MS: *m*/*z* = 168 $[M+1]^+$.

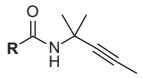
4.1.2. *N*-[Formamido-(5-hydroxy-2-nitrophenyl)methyl]formamide (6)

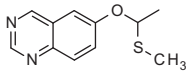
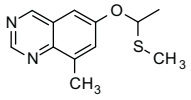
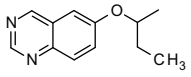
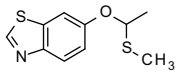
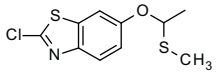
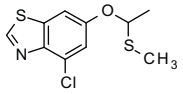
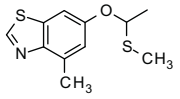
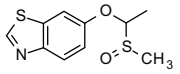
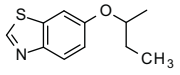
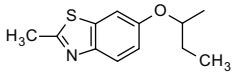
A stream of hydrogen chloride gas was bubbled through a light yellow suspension of 5-hydroxy-2-nitrobenzaldehyde (**5**, 6.7 g, 40 mmol) in 25 ml of formamide under stirring at room temperature. The temperature rose rapidly after starting the addition of hydrogen chloride and an orange solution formed when the temperature reached 50 °C. When the temperature reached 80 °C (20 min after initializing the gas flow), crystals started to precipitate. After the reaction temperature reached 90 °C, it was kept at this level with the help of external cooling. After cooling the reaction mixture for 30 min, the reaction temperature began to fall down when the cooling was stopped. The gas flow was turned off, the reaction mixture was allowed to cool down to room temperature and diluted with ice-water and treated with 30% aqueous sodium hydroxide solution until a pH value of 4 was reached. The resulting suspension was filtered, the solid residue was washed with water and dried to deliver *N*-[formamido-(5-hydroxy-2-nitrophenyl)methyl]formamide (**6**, 7.0 g, 29 mmol, 73%) as yellowish crystals. Mp, 239–240 °C. ^{1}H NMR (DMSO-d_6): δ = 6.85 (t, 1H), 6.97 (s, 1H), 7.06 (t, 1H), 7.92–8.01 (m, 2H), 8.88 (d, 1H), 10.99 (br s, 1H). LC–MS: Rt = 1.18 min; MS: *m*/*z* = 241 $[M+1]^+$, 242 $[M+2]^+$.

4.1.3. Quinazolin-6-ol (7)

20 ml of acetic acid were added dropwise to a suspension of *N*-[formamido-(5-hydroxy-2-nitrophenyl)methyl] formamide (**6**, 4.8 g, 20 mmol) and zinc powder (15 g, 0.23 mol) in 75 ml of crushed ice. The reaction mixture was stirred for 30 min, then additional zinc powder (5.8 g, 90 mmol) was added portionwise. During this addition the reaction temperature rose to 30 °C. The reaction mixture was stirred for 3 h at room temperature. The resulting grey suspension was filtered through celite. The filtrate was neutralized by addition of solid sodium bicarbonate and

Table 2
Influence of the substitution pattern on the anti-oomycete activity[a]



Entry	R	*Phytophthora infestans* (potato late blight)	*Plasmopara viticola* (grape downy mildew)	*Pythium ultimum* (damping-off disease)
1 (**2**)		74	80	50
2 (**22**)		94	100	24
3		0	50	55
4		100	100	0
5		0	0	0
6 (**3**)		99	100	20
7		100	100	80
8		0	0	0
9		35	80	18
10		0	0	0

[a] Results are given in % activity at 60 ppm for *Phytophthora infestans* and *Plasmopara viticola* and at 20 ppm for *Pythium ultimum*.

extracted with a 95:5 mixture of ethyl acetate and methanol. The combined organic layer was dried over magnesium sulfate and evaporated to directly deliver quinazolin-6-ol (**7**, 2.8 g, 19 mmol, 96%). ^{1}H NMR (DMSO-d_6): δ = 7.23 (d, 1H), 7.51 (dd, 1H), 7.82 (d, 1H), 9.01 (s, 1H), 9.40 (s, 1H), 10.56 (br s, 1H). LC–MS: Rt = 1.38 min; MS: m/z = 147 $[M+1]^+$.

4.1.4. Methyl 2-quinazolin-6-yloxybutanoate (8)

Potassium carbonate (8.3 g, 60 mmol) was added to a solution of quinazolin-6-ol (**7**, 2.9 g, 20 mmol) in 50 ml of *N*,*N*-dimethylformamide. After the addition of methyl 2-bromobutyrate (4.5 g, 25 mmol), the reaction mixture was stirred for 16 h at room temperature. Subsequently the dark brown mixture was poured on a cold saturated aqueous solution of sodium bicarbonate and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by chromatography on silica gel, using ethyl acetate and heptane as eluents to yield methyl 2-quinazolin-6-yloxybutanoate (**8**, 3.2 g, 13 mmol, 65%). ^{1}H NMR ($CDCl_3$): δ = 1.14 (t, 3H), 2.10 (q, 2H), 3.79 (s, 3H), 4.77 (t, 1H), 7.04 (d, 1H), 7.63 (dd, 1H), 8.00 (d, 1H), 9.21 (s, 1H), 9.28 (s, 1H). LC–MS: Rt = 1.40 min; MS: m/z = 247 $[M+1]^+$.

4.1.5. *N*-(1,1-Dimethylprop-2-ynyl)-2-quinazolin-6-yloxy-butanamide (9)

A solution of methyl 2-quinazolin-6-yloxybutanoate (**8**, 1.5 g, 6.1 mmol) in 30 ml of ethanol was treated with 4.6 ml of a 2 N solution of sodium hydroxide in water. The reaction mixture was stirred for 1 h at room temperature, then poured on ice-water and acidified to pH 2 by addition of 2 N hydrochloric acid. The mixture was extracted with ethyl acetate, the organic layer was washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure to deliver 2-quinazolin-6-yloxybutanoic acid. 1,1-Dimethylprop-2-ynylamine (0.34 g, 4.1 mmol) was dissolved in 30 ml of *N*,*N*-dimethylformamide and triethylamine (0.41 g, 4.1 mmol), 1-hydroxy-7-azabenzotriazole (0.55 g, 4.1 mmol), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (0.78 g, 4.1 mmol) and the above prepared 2-quinazolin-6-yloxybutanoic acid (0.95 g, 4.1 mmol) were added consecutively. The reaction mixture was stirred for 20 h at room temperature, then poured on saturated aqueous sodium bicarbonate solution and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate and evaporated under reduced pressure, the residue was purified by chromatography on silica gel, using ethyl acetate and heptane as eluents to deliver *N*-(1,1-dimethylprop-2-ynyl)-2-quinazolin-6-yloxy-butanamide (**9**, 1.0 g, 3.4 mmol, 55%).

^{1}H NMR ($CDCl_3$): δ = 1.07 (t, 3H), 1.61 (s, 3H), 1.63 (s, 3H), 2.06 (q, 2H), 2.32 (s, 1H), 4.61 (t, 1H), 6.35 (br s, 1H), 7.20 (d, 1H), 7.64 (dd, 1H), 8.02 (d, 1H), 9.27 (s, 1H), 9.32 (s, 1H). LC–MS: Rt = 1.48 min; MS: m/z = 298 $[M+1]^+$.

4.1.6. Methyl 2-methylsulfanyl-2-quinazolin-6-yloxyacetate (10)

Methyl 2-chloro-2-(methylsulfanyl)acetate (1.7 g, 11 mmol) and milled potassium carbonate (5.0 g, 36 mmol) were consecutively added to a suspension of quinazolin-6-ol (**7**, 1.0 g, 7.2 mmol) in 15 ml of *N*,*N*-dimethylformamide. The reaction mixture was stirred for 4 h at room temperature, then poured on a cold saturated aqueous solution of sodium bicarbonate and extracted with ethyl acetate. The organic layer was washed with water, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by chromatography on silica gel, using ethyl acetate and hexane as eluents to deliver methyl 2-methylsulfanyl-2-quinazolin-6-yloxyacetate (**10**, 1.2 g, 4.4 mmol, 61%). ^{1}H NMR ($CDCl_3$): δ = 2.25 (s, 3H), 3.90 (s, 3H), 5.78 (s, 1H), 7.31 (d, 1H), 7.70 (dd, 1H), 8.03 (d, 1H), 9.25 (s, 1H), 9.36 (s, 1H). LC–MS: Rt = 1.36 min; MS: m/z = 265 $[M+1]^+$.

4.1.7. 2-Methylsulfanyl-2-quinazolin-6-yloxy-acetic acid (11)

A suspension of methyl 2-methylsulfanyl-2-quinazolin-6-yloxyacetate (**10**, 1.1 g, 4.1 mmol) in 15 ml of ethanol was treated with 3.1 ml of a 2 N solution of sodium hydroxide in water. The reaction mixture was stirred for 1 h at room temperature, then cooled down to 0 °C, acidified with 2 N hydrochloric acid until pH 5 was reached and evaporated. The remainder was suspended in ethanol and stirred for 10 min at 60 °C. The suspension was filtered, the solid residue washed with cold ethanol and dried to deliver 2-methylsulfanyl-2-quinazolin-6-yloxy-acetic acid (**11**, 1.0 g, 4.0 mmol, 97%). ^{1}H NMR (DMSO-d_6): δ = 2.06 (s, 3H), 5.44 (s, 1H), 7.40 (d, 1H), 7.63 (dd, 1H), 7.84 (d, 1H), 9.08 (s, 1H), 9.37 (s, 1H). LC–MS: Rt = 1.13 min; MS: m/z = 251 $[M+1]^+$.

4.1.8. *N*-(1,1-dimethylbut-2-ynyl)-2-methylsulfanyl-2-quinazolin-6-yloxy-acetamide (2)

Triethylamine (0.5 g, 5 mmol), 1-hydroxy-7-azabenzotriazole (0.34 g, 2.5 mmol), 1-ethyl-3-(3-dimethylamino-propyl)carbodiimide (0.48 g, 2.5 mmol) and 2-methylsulfanyl-2-quinazolin-6-yloxy-acetic acid (**11**, 0.62 g, 2.5 mmol) were added consecutively to a solution of 1,1-dimethylbut-2-yn-1-amine (0.33 g, 2.5 mmol) in 10 ml of *N*,*N*-dimethylformamide. The reaction mixture was stirred for 16 h at room temperature, then poured on saturated aqueous sodium bicarbonate solution and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate and evaporated under reduced pressure, the residue was purified by chromatography on silica gel, using ethyl acetate and hexane as eluents to deliver *N*-(1,1-dimethylbut-2-ynyl)-2-methylsulfanyl-2-quinazolin-6-yloxy-acetamide (**2**, 0.48 g, 1.4 mmol, 58%). ^{1}H NMR ($CDCl_3$): δ = 1.69 (s, 6H), 1.83 (s, 3H), 2.22 (s, 3H), 5.66 (s, 1H), 6.69 (br s, 1H), 7.37 (d, 1H), 7.68 (dd, 1H), 8.05 (d, 1H), 9.28 (s, 1H), 9.36 (s, 1H). LC–MS: Rt = 1.51 min; MS: m/z = 330 $[M+1]^+$.

4.1.9. Methyl 2-amino-5-iodo-3-methyl-benzoate (13)

A mixture of 2-amino-5-iodo-3-methyl-benzoic acid (**12**, 15 g, 54 mmol) in 90 ml of methanol was treated dropwise with 81 ml of a 2 M solution of (trimethylsilyl)diazomethane in hexane. During the addition the temperature was not allowed to exceed 40 °C. The reaction mixture was stirred 2 h at room temperature, then the solvent was removed under reduced pressure to deliver methyl 2-amino-5-iodo-3-methyl-benzoate (**13**, 15.6 g, 54 mmol, 99%), which was pure enough to be directly used in the next step. ^{1}H NMR (acetone-d_6): δ = 2.03 (s, 3H), 3.69 (s, 3H), 6.32 (br s, 2H), 7.33 (s, 1H), 7.82 (s, 1H). LC–MS: Rt = 1.87 min; MS: m/z = 292 $[M+1]^+$.

4.1.10. Methyl 2-(2,5-dimethylpyrrol-1-yl)-5-iodo-3-methyl-benzoate (14)

A mixture of methyl 2-amino-5-iodo-3-methyl-benzoate (**13**, 7.8 g, 27 mmol), acetonylacetone (4.3 g, 37 mmol) and catalytic amounts of *p*-toluenesulfonic acid in 125 ml of toluene was heated to reflux for 18 h, during which forming water was collected with the aid of a Dean-Stark trap. The reaction mixture was cooled to room temperature and diluted with aqueous ammonium chloride solution and ethyl acetate. The phase were separated, the organic layer was washed with a aqueous ammonium chloride solution, dried over magnesium sulfate and evaporated under reduced pressure, the residue was purified by chromatography on silica gel, using ethyl acetate and cyclohexane as eluents to deliver methyl 2-(2,5-dimethylpyrrol-1-yl)-5-iodo-3-methyl-benzoate (**14**, 8.3 g, 22 mol, 84%). ^{1}H NMR ($CDCl_3$): δ = 1.84 (s, 6H), 1.91 (s, 3H), 3.68 (s, 3H), 5.87 (s, 2H), 7.82 (d, 1H), 8.05 (d, 1H). LC–MS: Rt = 2.14 min; MS: m/z = 370 $[M+1]^+$.

4.1.11. Methyl 2-(2,5-dimethylpyrrol-1-yl)-5-methoxy-3-methyl benzoate (15)

Sodium (1.3 g, 56 mmol) was added to a solution of methyl 2-(2,5-dimethylpyrrol-1-yl)-5-iodo-3-methyl-benzoate (**14**, 6.9 g, 19 mmol) in 50 ml of methanol. The mixture was stirred for 1 h at room temperature, then it was diluted with 90 ml of *N*,*N*-dimethylformamide. Copper-bronze (2.4 g, 37 mmol) was added and the reaction mixture was stirred for 3 h at 130 °C. Subsequently the mixture was cooled to room temperature and filtered through Celite. The filtrate was washed with aqueous ammonium sulfate solution, the aqueous layer was extracted with ethyl acetate. The combined organic layer was dried over magnesium sulfate and evaporated under reduced pressure, the residue was purified by chromatography on silica gel, using ethyl acetate and cyclohexane as eluents to deliver methyl 2-(2,5-dimethylpyrrol-1-yl)-5-methoxy-3-methyl benzoate (**15**, 3.1 g 11 mol, 62%). ^{1}H NMR ($CDCl_3$): δ = 1.87 (s, 6H), 1.92 (s, 3H), 3.66 (s, 3H), 3.87 (s, 3H), 5.87 (s, 2H), 6.99 (d, 1H), 7.24 (d, 1H). LC–MS: Rt = 1.97 min; MS: m/z = 274 $[M+1]^+$.

4.1.12. Methyl 2-amino-5-methoxy-3-methyl benzoate (16)

A solution of methyl 2-(2,5-dimethylpyrrol-1-yl)-5-methoxy-3-methyl-benzoate (**15**, 3.0 g 11 mmol), hydroxylamine hydrochloride (13 g, 0.19 mol) and triethylamine (3.3 g, 33 mol) in 100 ml of a 2:1 ethanol/water mixture was irradiated under microwave conditions for 1 h at 180 °C. Subsequently, the reaction mixture was cooled and concentrated in vacuo. The remainder was taken up in water and ethyl acetate, the phases were separated and the organic layer was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure, the residue was purified by chromatography on silica gel, using ethyl acetate and cyclohexane as eluents to deliver methyl 2-amino-5-methoxy-3-methyl benzoate (**16**, 900 mg, 5.0 mmol, 45%). ^{1}H NMR ($CDCl_3$): δ = 2.16 (s, 3H), 3.75 (s, 3H), 3.88 (s, 3H), 6.89 (d, 1H), 7.26 (d, 1H). LC–MS: Rt = 1.47 min; MS: m/z = 196 $[M+1]^+$.

4.1.13. 6-Methoxy-8-methyl-1*H*-quinazolin-4-one (17)

Formamidine acetate (6.2 g, 60 mmol) was added to a solution of methyl 2-amino-5-methoxy-3-methyl benzoate (**16**, 2.9 g, 14 mmol) in 100 ml of 2-methoxyethanol. The reaction mixture was heated for 16 h to reflux, then cooled down to room temperature and evaporated under reduced pressure. The remaining solid was taken up in a saturated aqueous sodium bicarbonate solution, filtered, washed with water and dried to deliver

6-methoxy-8-methyl-1*H*-quinazolin-4-one (**17**, 2.2 g, 12 mmol, 86%). ^{1}H NMR (DMSO): δ = 2.51 (s, 3H), 3.84 (s, 3H), 7.29 (d, 1H), 7.35 (d, 1H), 8.00 (s, 1H), 12.17 (br s, 1H). LC–MS: Rt = 1.20 min; MS: m/z = 191 $[M+1]^+$.

4.1.14. 4-Chloro-6-methoxy-8-methylquinazoline (18)

Phosphorus oxychloride (15.3 g, 0.1 mol) was added to a mixture of 6-methoxy-8-methyl-1*H*-quinazolin-4-one (**17**, 2.2 g, 12 mmol) and *N*,*N*-dimethylaniline (2.9 g, 24 mmol) at room temperature. The reaction mixture was stirred for 2 h at 70 °C, then cooled down to room temperature and evaporated in vacuo. The remainder was taken up in ethyl acetate and washed with saturated aqueous sodium bicarbonate solution. The organic layer was dried over magnesium sulfate and concentrated under reduced pressure to deliver 4-chloro-6-methoxy-8-methylquinazoline (**18**, 2.5 g, 12 mmol, 99%), which was pure enough to be directly used in the next step. ^{1}H NMR ($CDCl_3$): δ = 2.72 (s, 3H), 3.97 (s, 3H), 7.28 (d, 1H), 7.43 (d, 1H), 8.93 (s, 1H). LC–MS: Rt = 1.68 min; MS: m/z = 209 $[M+1]^+$.

4.1.15. 8-Methylquinazolin-6-ol (19)

10% Palladium on carbon (0.4 g, 0.4 mmol was added to a mixture of 4-chloro-6-methoxy-8-methylquinazoline (**18**, 2.1 g, 10 mmol) and triethylamine (1.4 g, 14 mmol) in 25 ml of ethyl acetate. The reaction mixture was stirred under a hydrogen atmosphere for 16 h at room temperature and then filtered through Celite. The filtrate was washed with aqueous saturated sodium bicarbonate solution, water and brine, dried over magnesium sulfate and concentrated under reduced pressure to deliver 1.2 g of 6-methoxy-8-methylquinazoline, which was dissolved in 60 ml of dichloromethane. Boron tribromide (9.1 g, 36 mmol) was added and then the reaction mixture was irradiated under microwave conditions for 1 h at 100 °C. Subsequently, the reaction mixture was cooled, diluted with ethyl acetate and neutralized with saturated aqueous sodium bicarbonate solution. The organic layer was washed with brine, dried over magnesium sulfate and concentrated under reduced pressure to deliver 8-methylquinazolin-6-ol (**19**, 1.1 g, 7.0 mmol, 70%), which was pure enough to be directly used in the next step. ^{1}H NMR ($CDCl_3$): δ = 2.69 (s, 3H), 7.16 (d, 1H), 7.47 (d, 1H), 9.14 (s, 1H), 9.40 (s, 1H), 10.32 (br s, 1H). LC–MS: Rt = 0.98 min; MS: m/z = 161 $[M+1]^+$.

4.1.16. Methyl 2-(8-methylquinazolin-6-yl)oxy-2-methylsulfanyl-acetate (20)

Methyl 2-chloro-2-(methylsulfanyl)acetate (1.7 g, 11 mmol) was added to a suspension of 8-methylquinazolin-6-ol (**19**, 1.1 g, 7.0 mmol) and milled potassium carbonate (3.8 g, 28 mmol) in 25 ml of *N*,*N*-dimethylformamide. The reaction mixture was stirred for 4 h at room temperature and then filtered. The filtrate was diluted with ethyl acetate. The organic layer was washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by chromatography on silica gel, using ethyl acetate and hexane as eluents to deliver methyl 2-(8-methylquinazolin-6-yl)oxy-2-methylsulfanyl-acetate (**20**, 1.2 g, 4.3 mmol, 62%). ^{1}H NMR ($CDCl_3$): δ = 2.25 (s, 3H), 2.77 (s, 3H), 3.88 (s, 3H), 5.74 (s, 1H), 7.11 (d, 1H), 7.56 (d, 1H), 9.27 (s, 2H). LC–MS: Rt = 1.50 min; MS: m/z = 279 $[M+1]^+$.

4.1.17. 2-(8-Methylquinazolin-6-yl)oxy-2-methylsulfanyl-acetic acid (21)

A suspension of methyl 2-(8-methylquinazolin-6-yl)oxy-2-methylsulfanyl-acetate (**20**, 1.2 g, 4.3 mmol) in 30 ml of ethanol was treated with 3.1 ml of a 2 N solution of sodium hydroxide in water. The reaction mixture was stirred for 1 h at room temperature, then cooled down to 0 °C, acidified with 2 N hydrochloric acid until pH 7 was reached and evaporated. The remainder was triturated with dichloromethane, the resulting mixture concentrated under reduced pressure to deliver 2-(8-methylquinazolin-6-yl)oxy-2-methylsulfanyl-acetic acid (**21**, 0.9 g, 3.4 mmol, 79%). ^{1}H NMR (DMSO-d_6): δ = 2.12 (s, 3H), 2.67 (s, 3H), 5.44 (s, 1H), 7.27 (d, 1H), 7.57 (d, 1H), 9.13 (s, 1H), 9.35 (s, 1H), 9.36 (s, 1H). LC–MS: Rt = 1.35 min; MS: m/z = 265 $[M+1]^+$.

4.1.18. *N*-(1,1-Dimethylbut-2-ynyl)-2-(8-methylquinazolin-6-yl)-oxy-2-methylsulfanyl-acetamide (22)

1,1-Dimethylbut-2-yn-1-amine (51 mg, 0.38 mmol) *N*-ethyldiisiopropylamine (0.12 g, 0.95 mmol), catalytic amounts of 4-dimethylaminopyridine and then benzotriazol-1-yloxy)tris (dimethylamino) phosphonium hexafluorophosphate (BOP, Castro's reagent, 0.19 g, 0.43 mmol) were added consecutively to a solution of 2-(8-methylquinazolin-6-yl)oxy-2-methylsulfanyl-acetic acid (**21**, 0.1 g, 0.38 mmol) in 7 ml of *N*,*N*-dimethylformamide. The reaction mixture was stirred for 3 h at room temperature, then poured on brine and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure, the residue was purified by chromatography on silica gel, using ethyl acetate and cyclohexane as eluents to deliver *N*-(1,1-dimethylbut-2-ynyl)-2-(8-methylquinazolin-6-yl)oxy-2-methylsulfanyl-acetamide (**22**, 0.1 g, 0.3 mmol, 79%). Mp 145–147 °C. ^{1}H NMR ($CDCl_3$): δ = 1.70 (s, 6H), 1.83 (s, 3H), 2.21 (s, 3H), 2.80 (s, 3H), 5.64 (s, 1H), 6.68 (br s, 1H), 7.17 (d, 1H), 7.52 (d, 1H), 9.29 (s, 2H). LC–MS: Rt = 1.64 min; MS: m/z = 344 $[M+1]^+$.

4.1.19. 4-Chloro-6-methoxy-1,3-benzothiazol-2-amine (24)

Potassium thiocyanate (14.3 g, 0.15 mol) was added to a solution of 2-chloro-4-methoxyaniline (**23**, 5.8 g, 37 mmol) in 60 ml of acetic acid. After stirring this mixture for 10 min at room temperature, a solution of bromine (5.9 g, 37 mmol) in 60 ml of acetic acid was added dropwise. The reaction mixture was stirred for 16 h at room temperature, then neutralized with aqueous ammonium hydroxide solution and extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure to deliver 4-chloro-6-methoxy-1,3-benzothiazol-2-amine (**24**, 2.8 g, 13 mmol, 36%). ^{1}H NMR (DMSO-d_6): δ = 3.78 (s, 3H), 6.96 (d, 1H), 7.35 (d, 1H), 7.82 (br s, 2H). LC–MS: Rt = 1.36 min; MS: m/z = 215 $[M+1]^+$.

4.1.20. 4-Chloro-6-methoxy-1,3-benzothiazole (25)

A solution of sodium nitrite (5.2 g, 75 mmol) in 20 ml of water was added dropwise at −10 °C to a solution of 4-chloro-6-methoxy-1,3-benzothiazol-2-amine (**24**, 2.7 g, 12 mmol) in 100 ml of 85% phosphorous acid under strong stirring. The mixture was stirred for 1 h at room temperature, then 38 ml of 50% hydrophosphorous acid were added dropwise at this temperature. The reaction mixture was stirred for 1 h at room temperature, then an aqueous sodium carbonate solution was added and the mixture was extracted with dichloromethane. The organic layer was washed with water, dried over magnesium sulfate and evaporated under reduced pressure, the residue was purified by chromatography on silica gel, using ethyl acetate and hexane as eluents to deliver 4-chloro-6-methoxy-1,3-benzothiazole (**25**, 1.2 g, 6.0 mmol, 48%). ^{1}H NMR ($CDCl_3$): δ = 3.90 (s, 3H), 7.21 (d, 1H), 7.33 (d, 1H), 8.90 (s, 1H). LC–MS: Rt = 1.56 min; MS: m/z = 200 $[M+1]^+$.

4.1.21. 4-Chloro-1,3-benzothiazol-6-ol (26)

15 ml of a 1 M solution of boron tribromide in dichloromethane were slowly added at −30 °C to a solution of 4-chloro-6-methoxy-1,3-benzothiazole (**25**, 1.0 g, 5.0 mmol) in 50 ml of dichloromethane. After the end of the addition the reaction mixture was allowed to reach room temperature and was stirred for 16 h at this temperature. 50 ml of methanol were slowly added and the

resulting mixture was stirred for further 16 h at room temperature. The mixture was concentrated in vacuo and the remainder was taken up in ethyl acetate. The organic layer was washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure to deliver 4-chloro-1,3-benzothiazol-6-ol (**26**, 0.9 g, 4.7 mmol, 94%). ^{1}H NMR (DMSO): δ = 7.09 (d, 1H), 7.43 (d, 1H), 9.18 (s, 1H), 10.21 (br s, 1H). LC–MS: Rt = 1.19 min; MS: m/z = 186 $[M+1]^+$.

4.1.22. Ethyl 2-[(4-chloro-1,3-benzothiazol-6-yl)oxy]-2-methylsulfanyl-acetate (27)

Milled potassium carbonate (1.5 g, 11 mmol) and ethyl 2-chloro-2-(methylsulfanyl)acetate (1.25 g, 5.9 mmol) were added consecutively to a suspension of 4-chloro-1,3-benzothiazol-6-ol (**26**, 0.9 g, 4.7 mmol) in 25 ml of *N*,*N*-dimethylformamide. The reaction mixture was stirred for 2 h at 60 °C, then poured on water and extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by chromatography on silica gel, using ethyl acetate and cyclohexane as eluents to deliver ethyl 2-[(4-chloro-1,3-benzothiazol-6-yl)oxy]-2-methylsulfanyl-acetate (**27**, 1.2 g, 3.8 mmol, 81%). ^{1}H NMR ($CDCl_3$): δ = 1.35 (t, 3H), 2.24 (s, 3H), 4.33 (q, 2H), 5.62 (s, 1H), 7.33 (d, 1H), 7.48 (d, 1H), 8.96 (s, 1H). LC–MS: Rt = 1.78 min; MS: m/z = 318 $[M+1]^+$.

4.1.23. 2-[(4-Chloro-1,3-benzothiazol-6-yl)oxy]-2-methylsulfanyl-acetic acid (28)

A suspension of ethyl 2-[(4-chloro-1,3-benzothiazol-6-yl)oxy]-2-methylsulfanyl-acetate (**27**, 1.2 g, 3.8 mmol) in 40 ml of tetrahydrofurane was slowly treated at 0 °C with 10 ml of a 0.5 N solution of sodium hydroxide in water. The reaction mixture was stirred for 1 h between 0 and 10 °C, then warmed to room temperature, poured on ethyl acetate and acidified with 1 N hydrochloric acid until pH 3 was reached. The mixture was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure to deliver 2-[(4-chloro-1,3-benzothiazol-6-yl)oxy]-2-methylsulfanyl-acetic acid (**28**, 1.0 g, 3.5 mmol, 91%). ^{1}H NMR (DMSO-d_6): δ = 2.13 (s, 3H), 6.07 (s, 1H), 7.45 (d, 1H), 7.86 (d, 1H), 9.33 (s, 1H). LC–MS: Rt = 1.60 min; MS: m/z = 290 $[M+1]^+$.

4.1.24. 2-[(4-Chloro-1,3-benzothiazol-6-yl)oxy]-*N*-(1,1-dimethyl-but-2-ynyl)-2-methylsulfanyl-acetamide (3)

1-Hydroxy-7-azabenzotriazole (66 mg, 0.5 mmol), 2-(1-H-benzotriazol-1-yl)-1,1,3,3,-tetramethyluronium tetrafluoroborate (TBTU, 0.15 g, 0.5 mmol) and 1,1-dimethylbut-2-yn-1-amine (65 mg, 0.5 mmol) were added consecutively to a solution of 2-[(4-chloro-1,3-benzothiazol-6-yl)oxy]-2-methylsulfanyl-acetic acid (**28**, 0.13 g, 0.5 mmol) and triethylamine (0.14 g, 1.4 mmol) in 8 ml of acetonitrile. The reaction mixture was stirred for 16 h at room temperature, then poured on saturated aqueous ammonium chloride solution and extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure, the residue was purified by chromatography on silica gel, using ethyl acetate and cyclohexane as eluents to deliver (**2**, 0.12 g, 0.4 mmol, 77%). ^{1}H NMR ($CDCl_3$): δ = 1.71 (s, 6H), 1.84 (s, 3H), 2.20 (s, 3H), 5.53 (s, 1H), 6.69 (br s, 1H), 7.32 (d, 1H), 7.50 (d, 1H), 8.99 (s, 1H). LC–MS: Rt = 1.77 min; MS: m/z = 369 $[M+1]^+$.

4.2. Biology

4.2.1. *Phytophthora infestans*/potato (activity against late blight on potato)

Two-week old potato plants cv. Bintje were sprayed in a spray chamber with the formulated test compounds diluted in water. Two days after application, the test plants were spray-inoculated with a sporangia suspension containing 50,000 spores/mL. The inoculated test plants were subsequently incubated in a growth chamber at 18 °C with 14 h light/day and 100% rh. The percentage leaf area covered by disease was assessed when an appropriate level of disease appeared on untreated check plants (5–7 days after application).

4.2.2. *Plasmopara viticola*/grape (activity against downy mildew on grapevine)

Three-week old grape seedlings cv. Gutedel were sprayed in a spray chamber with the formulated test compounds diluted in water. One day after application, the test plants were spray-inoculated on the lower leaf-surface with a sporangia suspension containing 70,000 spores/mL. The inoculated test plants were then incubated at 22 °C and 100% rh in a greenhouse and the percentage leaf area covered by disease was assessed when an appropriate level of disease appeared on untreated check plants (6–8 days after application).

4.2.3. *Pythium ultimum*/cotton (activity against damping-off on cotton)

A defined amount of mycelium of *P. ultimum* was mixed with water. The formulated test compounds were added to the mycelium suspension. The mixture was applied into a pouch equipped with a custom-built folded filter paper. After the application four cotton seeds cv. Millenium were sown into the upper fold of the filter paper. The prepared pouches were then incubated for 6 days at 17 °C with 14 h light/day and 100% rh followed by 4 days at 22 °C and 80% rh with a photo period of 14 h. The evaluation was made by visual assessment of the emergence and the level of disease on roots and shoot.

4.2.4. *Pythium ultimum* (activity in liquid culture)

A Mycelia fragments and oospores of a newly grown liquid culture of the fungus are directly mixed into nutrient broth (PDB potato dextrose broth). After placing a (DMSO) solution of test compound into a microtiter plate (96-well format), the nutrient broth containing the fungal mycelia/spore mixture is added. The test plates are incubated at 24 °C and the inhibition of growth is determined photometrically 2–3 days after application.

Acknowledgement

The authors gratefully acknowledge the excellent synthetic contribution of Myriam Baalouch, Thomas Grether, Nikola Kokosar, Jerome Sachet, Grit Schade and Thomas Steffen.

References and notes

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