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Original Article

2,4-Dioxo-1,3-thiazolidine derivatives as a lead for new fungicides

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Derivatives of 2,4-dioxo-5-benzylidene-3-thiazolidineacetamide were prepared and the fungicidal and the bactericidal activities of twenty-three related compounds were examined. *In vitro* tests at a concentration of 10 mg/l, some derivatives showed moderate or considerable inhibition against *Pyricularia oryzae* (*P. oryzae*), *Rhizoctonia solani* (*R. solani*), and *Septoria tritici*, but only modest activity against *Botrytis cinerea* and *Burkhorderia gluma*. The activity of a few compounds was enhanced by co-application of salicyl hydroxymate (SHAM), which is known to potentiate the fungicidal activity of strobilurins. In pot tests at a concentration of 500 mg/l, some compounds showed appreciable activity against rice blast, late blight on tomatoes, downy mildew on cucumbers, or leaf rust on wheat. Of these compounds *N*,*N*-dimethyl-2,4-dioxo-5-benzyl-3-thiazolidineacetamide completely removed the downy mildew. Most of them showed only modest activity against gray mold on cucumbers.

Keywords: 2,4-dioxothiazolidine, fungicide, bactericide, SHAM-test.

Introduction

It has been shown that fungicides and bactericides can be classified into forty six groups according to their modes of action.[1)] However, many fungicides are only available in a restricted number of regions and for certain crops because they are not registered everywhere or because the market for them is small, and so only a few modes of action dominate the fungicide market.[1)] With this in mind, fungicides that target a common fungi biochemical process would be likely to become widely available. Epalrestat is a diabetic mellitus medicine affecting aldose reductase, the first enzyme of the polyol pathway that catalyses the NADPH-dependent reduction of glucose to sorbitol.[2)] Recently 2,4-dioxo-5-phenylmethylene-3-thiazolidineacetic acid (cf. compound 1 in Fig. 1, in which the phenylbutadienyl group of epalrestat at the 5th position is replaced with an arylidene), was reported to display a potent pharmaceutical action.[3)] We have investigated the biochemical processes inhibited by this diabetic medicine because its primary process may also affect other organisms. Thus, we have decided to take up the arylidene derivative as the first substance in a study considering the chemical and photochemical stability of its skeleton and have investigated its fungicidal and bactericidal activity. This paper describes the activity of known 2,4-thiazolidinediones and related novel derivatives against various plant pathogens.

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Materials and Methods

1. Chemicals

All melting points (mp) are uncorrected. IR spectra were measured with a Perkin Elmer FTIR 1600 spectrometer. NMR spectra were obtained with a Varian Gemini 2000 C/H (400 MHz). Chemical shifts were recorded in δ (ppm) and the coupling constant in Hz. Mass spectra were recorded with a JEOL JMS-700. Compounds **1**–**6** were prepared according to the published procedures[3,4)]. The new compounds were prepared according to the schemes in Fig. 2 and the structures were identified spectroscopically (Tables 1–3).

1.1. Procedure A

N-Methyl-2,4-dioxo-5-phenylmethylene-3-thiazolidineacetamide (**8**)

A solution of **1**[4)] (263 mg, 1 mol) in dichloromethane (5 ml) was treated with thionyl chloride (3 ml), and the reaction mixture was stirred at room temperature for 1 hr before *ca.* 20 mg of DMF was added. The mixture became homogeneous after 5–6 hr. The resultant solution was slowly added to an ice-cold aq. 40% methylamine solution (10 ml). The mixture was stirred in an ice-water bath for 10 hr. The solvents were dis-

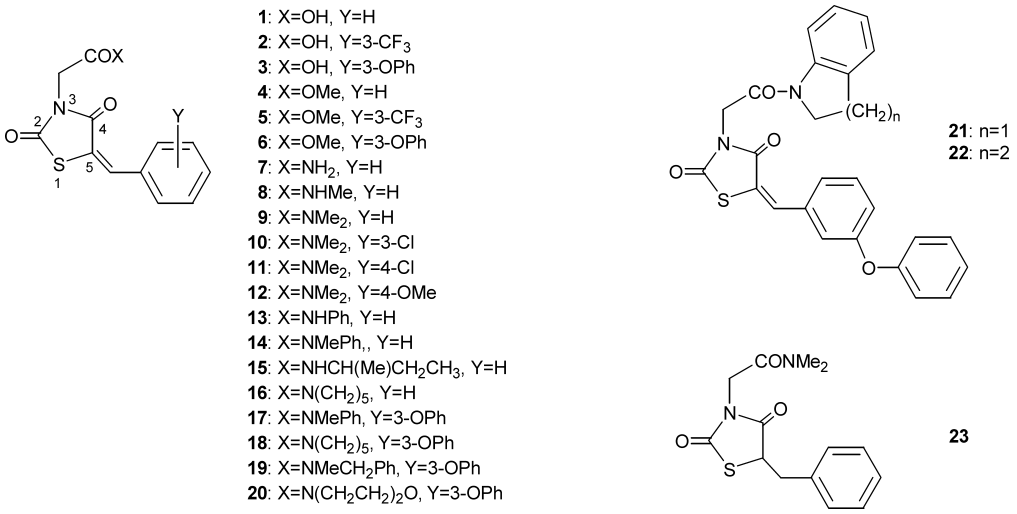


Fig. 1. The tested 2,4-dioxo-1,3-thiazolidine derivatives.

tilled off and the residual solid was crystallized from water and filtered. The product was obtained by recrystallization of the collected solid from ethanol. Yield: 223 mg (81%). HRMS (EI) *m*/*z* (M^+): Calcd. for $C_{13}H_{12}N_2O_3S$: 276.0569, Found: 276.0545.

Compound **7** was prepared according to this procedure using ammonia in place of methylamine solution.

1.2. Procedure B

N-{1-[2,4-Dioxo-5-(3-phenoxyphenylmethylene)-3-thiazolidinyl]acetyl}piperidine (**18**)

A solution of **3**[3] (355 mg, 1.0 mmol) in chloroform (10 ml) was treated with thionyl chloride (2 ml), and the reaction mixture was stirred at room temperature for 1 hr before *ca.* 20 mg of DMF was added. The mixture was then stirred at 50–60C° for 5–6 hr. The resultant solution was slowly added to an ice-cold piperidine solution (75 mg, 0.88 mmol) with triethylamine (202 mg, 2 mmol) in chloroform (20 ml), and the stirring was continued at ambient temperature for 10 hrs. The reaction mixture was poured into ice water, and then the organic phase was washed successively with 1% aq. HCl, water, 1% aq. NaOH, and water before being dried over $MgSO_4$. The solvent was distilled off and the residual solid was crystallized from methanol. Yield: 143 mg (34%). HRMS (EI) *m*/*z* (M^+): Calcd. for $C_{23}H_{22}N_2O_4S$: 422.1300, Found: 422.1325.

Compounds **13**, **15**, **16**, and **19**–**22** were prepared from the corresponding amine and acid chloride according to *Procedure B*.

1.3. Procedure C

N,N-Dimethyl-2,4-dioxo-5-phenylmethylene-3-thiazolidineacetamide (**9**)

A mixture of 2,4-dioxo-5-phenylmethylene-3-thiazolidine[3] (205 mg, 1 mmol), *N*,*N*-dimethyl-2-chloroacetamide (145 mg, 1.2 mmol), and potassium carbonate (278 mg, 2 mmol) was stirred in acetonitrile under reflux for 8 hr. The reaction mixture was cooled and filtered, and then the acetonitrile was distilled off. The residue was subjected to column chromatogra-

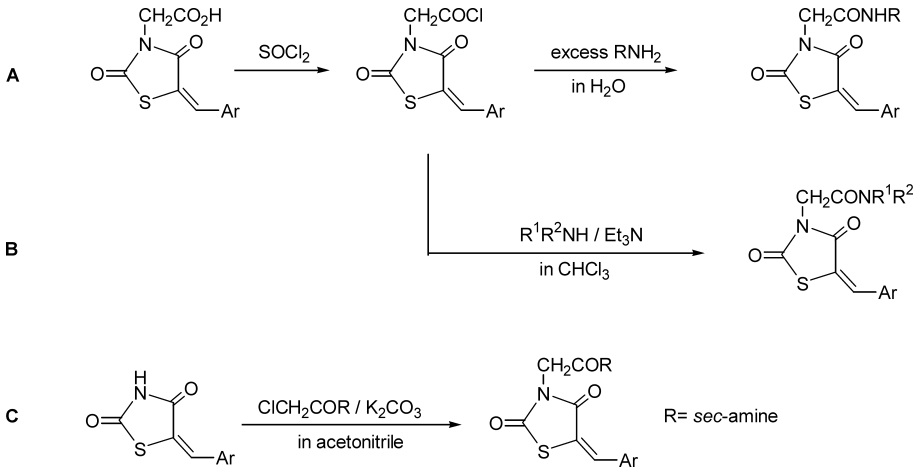


Fig. 2. The preparation scheme for the 2,4-dioxo-1,3-thiazolidine derivatives.

Table 1. Mp, IR, and MS data of the 5-arylidene-2,4-thiazolidinediones

Compound	Mp (°C)	CO and =CH-Ar absorptions [a]	EIMS *m/z* (%)[b]
7	234–236	1736, 1694, 1671, 1608	262 (M^+, 33), 134 ($C_6H_5CH=C=S$, 100)
8	223–225	1748, 1696, 1662, 1609	276 (M^+, 50), 134 ($C_6H_5CH=C=S$, 100)
9	193–195	1743, 1695, 1651, 1606	290 (M^+, 94), 134 ($C_6H_5CH=C=S$, 100)
10	191–192	1741, 1678, 1666, 1607	324 (M^+, 77), 168 (3-$ClC_6H_4CH=C=S$, 100)
11	214–215	1749, 1683, 1667, 1655, 1605	324 (M^+, 70), 168 (4-$ClC_6H_4CH=C=S$, 100)
12	210–211	1741, 1683, 1661, 1655, 1590	320 (M^+, 49), 164 (4-$MeOC_6H_4CH=C=S$, 100)
13	262–264	1748, 1729, 1697, 1664	338 (M^+, 62), 218 (48), 134 ($C_6H_5CH=C=S$, 100)
14	154–157	1745, 1719, 1681, 1658	352 (M^+, 74), 134 ($C_6H_5CH=C=S$ or C_6H_5NMeCO, 100)
15	245—248	1731(shoulder), 1696, 1659	318 (26), 134 ($C_6H_5CH=C=S$, 100)
16	167–169	1743, 1687, 1654, 1605	330 (M^+, 64), 134 ($C_6H_5CH=C=S$, 100)
17	50–52	1747, 1692 (broad)	444 (M^+, 80), 309 ($M^+-C_6H_5NMeCO$, 41) 226 (3-phenoxy–$C_6H_4CH=C=S$, 100)
18	116–118	1741, 1684, 1656, 1607	422 (M^+, 80), 225 ($C_6H_5OC_6H_4CH=C=S$, 100)
19	123–124	1748, 1696, 1685, 1654	458 (M^+, 48), 226 (3-phenoxy $C_6H_4CH=C=S$, 56), 120 ($N(Me)C_6H_5CH_2$, 100)
20	142–143	1748, 1690, 1666, 1610	424 (M^+, 82), 226 (C6H5OC6H4CH=C=S, 100)
21	136–139	1746, 1685, 1670, 1604	456 (M^+, 41), 310 (M^+-indolinyl-CO, 32), 226 ($C_6H_5OC_6H_4CH=C=S$, 24), 119 (indolinyl–CO, 100)
22	139–140	1744, 1685, 1670	470 (M^+, 72), 310 (M^+-tetrahydroquinolinyl-CO, 40), 226 ($C_6H_5OC_6H_4CH=C=S$, 41), 133 (tetarahydroquinolinyl-CO, 100)
23	129–131	1753, 1687, 1660	292 (M^+, 100), 131 ($C_6H_5CH_2CH=C=O$, 16), 91 ($C_6H_5CH_2$, 78)

[a] ν (cm^{-1}) KBr. [b] 70 eV

phy on SiO_2 with isopropyl ether followed by ethyl acetate as an eluent. The product was purified by recrystallization from methanol. Yield: 119 mg (41%). HRMS (EI) *m/z* (M^+): Calcd. for $C_{14}H_{14}N_2O_3S$: 290.0725, Found: 290.0708.

Compounds **10**–**12**, **14** and **17** were prepared from the reaction of the corresponding haloacetamides with 5-arylidene-2,4-thiazolidinedione and compound 23 was prepared from 5-benzyl-2,4-thiazolidinedione[5] with *N*,*N*-dimethyl-2-chloroacetamide according to *Procedure C*.

2. *Biological assay*

2.1. *In vitro tests*

2.1.1 *Fungicidal and bactericidal assay on a microplate*

Potato dextrose liquid medium (Difco) containing *Pyricularia oryzae* (*P. oryzae*: 1×10^4 spores/ml), *Botrytis cinerea* conidia (*B. cinerea*: 1×10^4 spores/ml), *Rhizoctonia solani* (*R. solani*: 1×10^4 fragments/ml), or *Septoria tritici* mycelia fragments (*S. tritici*: 1×10^4 fragments/ml) were prepared. For the sensitivity test, broth (Nissui) containing *Burkhorderia gluma* bacterial cells (*B. gluma*: 1×10^4 cells/ml) was prepared. Each test compound in DMSO (1 mg/ml) was diluted with these mediums to a concentration of 10 mg/l. One hundred microliters of test solution was added to a 96-well microtiter plate and the treated plate was incubated at 25°C for *P. oryzae*, *B. cinerea*, *R. solani*, and *S. tritici*, and at 30°C for *B. gluma*. The growth inhibition was evaluated by measuring the OD600 using a microplate reader (Biorad) after 1 day of incubation for *B. gluma*; 3 days for *P. oryzae*, *B. cinerea*, and *R. solani*; and 7 days for *S. tritici*. The inhibition rates are given as percentages in Table 4.

2.1.2. *Salicyl hydroxymate (SHAM) test*

The SHAM test was carried out to evaluate the inhibitory activity of each compound against the electron transport chain in *P. oryzae* and *R. solani*. One microliter of SHAM solution in DMSO (100 mM) was diluted with the test solution described in 2.1.1 to a concentration of 1 mM. The growth inhibition rates are given as percentages in Table 5.

2.2. *Fungicidal assay by foliar spraying on pot*

The fungicidal activities of the various test compounds on rice blast, tomato late blight, downy mildew, cucumber gray mold, and wheat leaf rust were tested. A solution containing 500 mg/l of test compound, 10% (v/v) of acetone, and 60 mg/l of surfactant (Gramin®-S, Sankyo) was sprayed onto plastic pots containing rice (Koshihikari), cucumbers (SHARP 1), tomatoes (Fukuzyu-2 gou), or wheat (Norin-61 gou) in fertilized soil. After air-drying, the plants were inoculated with the conidial solutions of *P. oryzae*, *P. infestans*, *Pseudoper-*

Table 2. Mp and the ^{1}H-NMR data of the 5-arylidene-2,4-thiazolidinediones[a)]

Compound	=CH-Ar[b)]	Aromatic	Others
7[c)]	7.91	7.50–7.59 (3H, m), 7.64–7.67 (2H. m)	4.25 (2H, s), 7.34 (1H, bs, NH), 7.76 (1H, bs, NH)
8	7.91	7.38–7.53 (5H, m)	2.59 (3H, bs), 4.40 (2H, s), 7.31 (1H, bs, NH)
9	7.92	7.45–7.53 (5H, m)	2.98 (3H, s), 3.09 (3H, s), 4.55 (2H, s)
10	7.84	7.39–7.42 (3H, m), 7.48 (1H, d, *J*=2.2)	2.99 (3H, s), 3.09 (3H, s), 4.54 (2H)
11	7.86	7.45 (4H, bs)	2.98 (3H, s), 3.09 (3H, s), 4.54 (2H)
12	7.87	6.99 (2H, dd, *J*=6.8/1.9), 7.37 (2H, dd, *J*=6.8/1.9)	2.98 (3H, s), 3.09 (3H, s), 3.86 (3H, s), 4.53 (2H)
13[c)]	8.00	7.33–7.67 (10H, m)	4.53 (2H), 7.08 (1H, bs, NH)
14	7.90	7.36–7.53 (10H, m)	3.31 (3H), 4.23 (2H, s)
15[c)]	7.97	7.51–7.56 (3H, m), 7.65 (2H, m),	0.83 (3H, t, *J*=7.1), 1.10 (3H, m), 1.39 (2H, m), 3.67 (1H, m),4.26 (2H, s), 8.07 (1H, d, *J*=7.6, NH)
16	7.92	7.40–7.53 (5H, m)	1.58–1.67 (6H, m), 3.43 (2H, m), 3.55-3.57(2H, s), 4.54 (2H, s)
17	7.82	7.04–7.08 (4H, m), 7.16–7.25 (2H, m), 7.26 (1H, s), 7.35–7.50 (7H, m)	3.30 (3H), 4.21 (2H, s)
18	7.84	7.05–7.09 (4H, m), 7.16–7.23 (2H, m), 7.37–7.44 (3H, m)	1.56–1.67 (6H, m), 3.42 (2H, m), 3.53-3.56(2H, s), 4.52 (2H, s)
19	7.87	7.05–7.43 (12H, m), 7.65 (2H, m)	2.97 (3H, s), 4.57 (2H, s), 4.59 (2H, s)
20	7.85	7.05–7.44 (9H, m)	3.51 (2H, m), 3.62 (2H, m), 3.71(2H, m), 3.76 (2H, m), 4.52 (2H, s),
21	7.88	7.03–7.45 (13H, m)	3.29 (2H, t, *J*=8.5), 4.16 (2H, t, *J*=8.5), 4.59 (2H, s)
22	7.83	7.06–7.39 (13H, m)	2.00 (2H, bs), 2.78 (2H, bs), 3.82 (2H, bs), 4.62 (2H, s)
23	–	7.24–7.33 (5H, m)	2.96 (3H, s), 3.04 (3H, s), 3.09 (1H, dd, *J*=13.7/10.9), 3.67 (1H, dd, *J*=13.7/4.0), 4.38 (2H, s), 4.53 (1H, dd, *J*=10.9/4.0)

[a)] The NMR was measured in $CDCl_3$ unless otherwise stated; *J* was measured in Hz; [b)] Singlet. [c)] NMR solvent: DMSO-d_6.

onospora cubensis, *B. cinerea*, and *Puccinia reconditq* to induce rice blast, late blight, downy mildew, gray mold, and leaf rust, respectively. The inoculated plants were incubated in a high-humidity incubator at 20°C for the gray mold, late blight, and downy mildew, and at 25°C for the rice blast and leaf rust. The damage rates were evaluated for the gray mold and late blight after 4 days of incubation, and after 7 days for the rice blast and downy mildew. The evaluation was carried out for leaf rust after the inoculated plants were first incubated in a high-humidity incubator for 1 day, and then in a greenhouse at 25°C for 10 days. The control indexes were ranked from zero to 5 according to the diseased leaf area (DA) percentage as follows

Rank:	0	1	2	3	4	5
DA(%):	∼0	<20	≥20–<40	≥40–<60	≥60–<80	≥80

The results are shown in Table 6.

Results and Discussion

Bruno *et al.* reported that the inhibitory effect of 2,4-dioxo-5-arylidenethiazolidine-3-acetic acids on bovine lens aldose reductase reached micro molar levels *in vitro*.[3)] Discouragingly, however, the efficacies of compounds **1**–**3** against the tested pathogens were almost nil in cases of using a 10 ppm (≒38 μM) treatment (Table 4). The esterification of compounds **4**–**6** resulted in a moderate fungicidal action of 60 to 90% control of *S. tritici*, which may be due to the increased lipophilicity. The activity was not observed in the benzylidene acetamides (**7**–**9**). Interestingly, however, the introduction of a chlorine atom or a methoxy group to the benzylidenyl phenyl ring of compound **9** produced significant fungicidal results (**10**–**12**). These compounds displayed good to high efficacy against the *Rhizoctonia*, and bactericidal activity on the *Burkhorderia*. Although most modifications of the amide part led to only modest activity enhancement, as shown by compounds **13**–**15**, a piperidine derivative (**16**) produced high septicidal activity. Interestingly, the 3-phenoxy substituent on the phenyl ring (compounds **18** and **19**) had no activity against *Septoria* fungus, but an increasing effect on *P. oryzae* (compounds **18**–**20**). The morpholino derivative (**20**) inhibited the fungus growth by 90%. The attachment of a

Table 3. ^{13}C-NMR data of the 5-arylidene-2,4-thiazolidinediones[a)]

Compound	=CH-Ar+Aromatic	C_5	C=O	Others
7[c)]	129.4, 130.1, 130.7, 132.9, 133.3	121.2	165.2, 166.8, 167.1	43.3
8	129.3, 130.2, 130.6, 133.2, 134.1	121.5	165.8, 166.0, 167.7	26.2, 43.7
9	129.0, 130.0, 130.4, 133.0, 134.0	121.2	164.1, 165.8, 167.7	35.6, 36.0, 42.3
10	128.0, 130.1, 130.4, 130.5, 132.5, 135.1, 135.4	123.3	164.2, 165.9, 167.5	36.0, 36.3, 42.7
11	129.6, 131.4, 131.8, 132.9, 136.7	122.2	164.2, 166.0, 167.6	36.0, 36.3, 42.7
12	114.9, 118.5, 132.3, 134.3, 162.6	126.0	164.2, 166.3, 168.2	35.9, 36.3, 42.6, 55.6
13[c)]	119.7, 124.3, 129.4, 130.0, 130.8, 131.4, 133.4, 134.2, 138.9	121.6	164.3, 165.9, 167.7	44.6
14	127.4, 128.7, 129.2, 130.2, 130.3, 130.5, 133.2, 134.1, 142.1	121.4	164.6, 165.9, 167.7	37.7, 43.0
15[c)]	129.4, 130.2, 130.8, 133.0, 133.3	121.3	164.2, 165.4, 167.1	10.8, 20.2, 28.9, 43.5, 46.3
16	129.2, 130.2, 130.5, 133.2, 134.2	121.5	162.5, 166.1, 168.0	24.3, 25.2, 26.1, 42.4, 43.4, 45.8
17	119.2, 119.5, 120.4, 122.3, 127.4, 128.3, 128.7, 130.0, 130.3, 130.5, 133.4, 134.9, 142.1, 156.2, 158.3	124.2	164.5, 165.8, 167.6	37.7, 43.0
18	119.2, 119.6, 120.4, 122.4, 124.6, 130.0, 130.5, 133.5, 134.9, 156.1, 158.3	124.2	162.4, 166.0, 167.8	24.3, 25.2, 26.2, 42.5, 43.5, 45.8
19	119.3, 119.7, 120.5, 126.5, 127.8, 128.3, 128.8, 129.3, 130.1, 130.6, 133.8, 134.9, 136.4, 156.2, 158.4	124.3	164.6, 166.0, 167.9	34.4, 42.6, 51.7
20	119.2, 119.6, 120.5, 122.2, 124.6, 130.0, 130.5, 133.8, 134.8, 156.1, 158.3	124.2	163.0, 165.8, 167.7	42.2, 42.5, 45.1, 66.2, 66.6
21	117.1, 119.2, 119.6, 120.5, 122.2, 124.4, 124.5, 124.6, 127.7, 128,8, 130.0, 130.5, 133.5, 133.9, 134.8, 156.1, 158.4	124.2	162.0, 165.8, 167.7	28.2, 43.7, 46.9
22	117.1, 119.2, 119.6, 120.4, 122.3, 124.6, 124.7, 126.5, 127.5, 128.9, 130.0, 130.5, 133.6, 134.8, 138.0, 156.1, 158.3	124.2	165.8, 167.6	23.7, 26.6, 43.5
23	127.6, 128.9, 129.1, 136.6, 134.0	–	164.3, 171.1, 173.9	35.9, 36.2, 39.3, 42.4, 52.1

[a)] In $CDCl_3$ unless otherwise stated; *J* was measured in Hz; [b)] Singlet. [c)] Solvent: DMSO-d_6.

phenyl group (compounds **13**, **14** and **17**) or a benzyl to the acetamidyl *N*-atom or annelation of the amide moiety (compounds **21** and **22**) tended to reduce the activity against the fungi. Replacement of the benzylidene with a benzyl group (compound **23**) did not enhance the inhibitory effect, either.

Strobilurins perform their fungicidal effects by blocking the electron flow in the mitochondrial respiration system, and the existence of a strobilurin-insensitive terminal oxidase in this complex system that allows flowing electrons through a bypass allows the fungi to grow.[6)] Salicylhydroxyamic acid (SHAM) is an inhibitor of this terminal oxidase, and there are several lines of evidence that suggest that fungicides with SHAM added to them potentiate strobilurin activity *in vitro*.[6–9)] We noticed a thiazolidine-dione bearing a motif (O=C–N–C=O) common to strobilurin famoxadone (Fig. 3), thus we attempted to clarify whether SHAM can exhibit a similar effect on the compounds in this study (Table 5). In fact, the growth inhibition rate for both *P. oryzae* and *R. solani* of compound **14** was enhanced almost to the level of metconazole by mixing it with SHAM. Furthermore, SHAM-treated compound **5** inhibited the growth of *R. solani*, and compound **15** had its efficacy elevated from 11 to 40%. This effect of SHAM is probably due to the common moiety of these compounds, but a question remains as to why only these molecules among the tested ones exhibited this effect.

The fungicidal results from the pot tests are given in Table 6. The morpholino derivative (**20**) controlled the blast disease on rice effectively, which is consistent with the *in vitro* result. Also, the *N*-methylanilide derivative (**17**) attained a good score. The other tested compounds gave lower efficacy against

Table 4. *In vitro* fungicidal and bactericidal results of the 5-arylidene-2,4-thiazolidinediones[a)]

Compound	Growth inhibition (%)				
	P. orizae	*R. solani*	*S. Tritici*	*B. cinerea*	*B. glumae*
1	0	15	0	0	0
2	10	2	29	1	18
3	9	0	18	0	19
4	0	16	68	12	8
5	0	3	62	0	20
6	25	8	86	24	35
7	10	0	40	0	19
8	15	0	28	0	10
9	0	4	0	0	18
10	14	76	10	0	47
11	21	82	20	0	51
12	10	68	12	0	0
13	0	22	33	0	19
14	42	16	47	19	22
15	15	0	57	3	18
16	0	21	86	31	17
17	38	0	4	0	11
18	61	0	0	10	8
19	43	0	4	0	15
20	90	0	35	27	0
21	0	0	0	21	4
22	18	0	0	0	10
23	22	51	4	0	49
Metconazole	99	100	100	98	15

[a)] Dose: 10 mg/l. On a microplate.

Table 5. *In vitro* fungicidal results of the 5-arylidene-2,4-thiazolidinediones[a)] after SHAM was added[b)]

Compound	Growth inhibition (%, with SHAM/without SHAM)	
	P. oryzae	*R. solani*
1	6/0	0/12
2	0/0	37/25
3	18/12	0/17
4	3/0	0/11
5	9/2	40/0
6	33/8	0/0
7	4/0	0/0
8	2/0	0/11
9	8/0	0/14
14	85/10	85/27
15	0/0	40/11
16	4/1	0/14
Metconazol	98/98	99/99

[a)] Dose: 10 mg/l. On a microplate. [b)] 1 mM SHAM added.

Table 6. *In vivo* fungicidal results of the 5-arylidene-2,4-thiazolidinediones[a)]

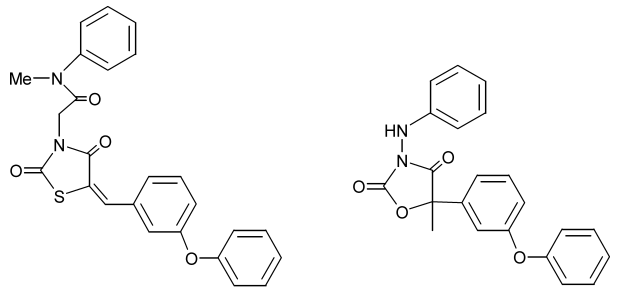
Compound	Control rate[b)]				
	PYROR[c)]	PHYTIN[d)]	PSPEPO[e)]	PUCCRT[f)]	BOTRCI[g)]
1	NT	5.0	1.5	2.5	4.7
2	NT	1.5	5.0	4.5	4.5
3	NT	1.5	4.0	1.0	4.1
4	NT	5.0	5.0	4.0	2.8
5	NT	2.5	5.0	3.0	4.3
6	NT	4.0	5.0	4.0	4.3
7	NT	1.5	5.0	4.5	3.8
8	NT	3.0	5.0	3.5	4.5
9	NT	3.5	1.0	0.5	4.6
10	1.5	5.0	1.5	1.0	5.0
11	1.5	5.0	5.0	1.5	5.0
12	1.5	5.0	5.0	4.0	5.0
13	NT	4.5	5.0	4.0	4.0
14	NT	1.0	5.0	2.0	2.4
15	NT	2.0	5.0	4.5	4.5
16	NT	1.0	3.0	2.0	4.5
17	0.5	5.0	1.5	5.0	1.5
18	1.2	5.0	1.0	3.5	5.0
19	2.0	5.0	4.0	3.0	2.0
20	0.5	1.0	1.0	5.0	2.0
21	NT	5.0	2.5	3.0	5.0
22	NT	5.0	1.0	1.0	5.0
23	NT	1.0	0.0	5.0	4.0
Fthalide[h)]	0.0	NT	NT	NT	NT
Maneb[i)]	NT	0.0	0.0	0.0	NT
Fludioxonil[j)]	NT	NT	NT	NT	0.0

[a)] Dose: 500 mg/l; onto a pot. NT stands for not tested. [b)] Rate 1–5 (See Text). [c)] Blast on rice. [d)] Late blight on tomato. [e)] Downy mildew on cucumber. [f)] Leaf rust on wheat. [g)] Gray mold on cucumber. [h)] 200 mg/l. [i)] 250 mg/l. [j)] 200 mg/l.

rice blast then compounds **17** and **20**. For the late blight on the tomatoes, compounds **14**, **16**, **20**, and **23** showed an appreciable effect, and the efficacies of compounds **2**, **3**, and **7** were considerable.

The complete control obtained by a benzyl derivative (**23**) and the good activity shown by morpholino thiazolidinedione (**20**) against the downy mildew on cucumber and the *phytophthora* is worth noting, considering that both diseases are caused by the same class of pathogen (*oomycetes*). These compounds may serve as a starting point for the development of fungicides against *oomycetes*. Interestingly, compounds **1**–**3**, **7**, **9**, **10**, **14**–**18**, **21**, and **22** were effective against either late blight or downy mildew.

Compound **9** controlled the leaf rust on wheat well. The acetic acid derivative (**3**) and the tetrahydroquinoline derivative (**22**), which hardly displayed any fungicidal effects *in vitro*, controlled the leaf rust significantly. It is a reminder that



14 famoxadone

Fig. 3. The structures of compound **14** and famoxadone.

in vitro fungicidal potency is not always reflected *in vivo*. For the Botrytis disease on cucumbers, no compounds of this type produced a notable effect except compound **17**.

None of the presented compounds surpassed the standard products in the fungicidal and bactericidal tests, but some compounds showed an apparent fungicidal tendency. We had started this work by referring to a pharmaceutical substance which is known as an aldose reductase inhibitor. However, now that the SHAM test suggested a possible respiration inhibitory action for some compounds, we are devising molecules by switching our viewpoint from the structure of the diabetic mellitus medicine to the O=C–N–C=O motif of strobilurin.

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