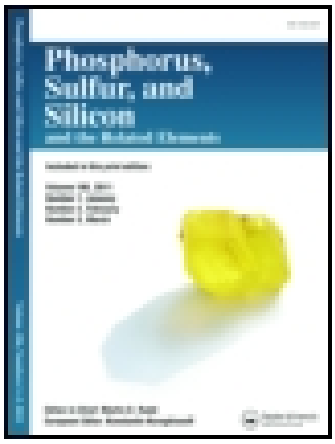

Phosphorus, Sulfur, and Silicon and the Related Elements

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Synthesis and Fungicidal Activity of Simple Structural 1,3-Thiazolidine-2-thione Derivatives.

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SYNTHESIS AND FUNGICIDAL ACTIVITY OF SIMPLE STRUCTURAL 1,3-THIAZOLIDINE-2-THIONE DERIVATIVES.

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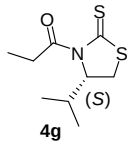
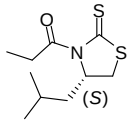
Abstract A series of simple structural 1,3-thiazolidine-2-thione derivatives with various substituents on the *S*-, *N*-, 4-, and 5-positions was synthesized with high yields from various vicinal amino alcohols *via* two steps and screened for their antifungal activity. Bioassay results reveal that some thiazolidine-2-thione derivatives show strong antifungal activities against *P. capsici*, *G. zeae*, *S. sclerotiorum*, *A. alternate*, *B. cinerea*, or *R. solani*. The SAR analysis indicates that *N*-acyl substituted and 4-alkyl substituents can enhance the antifungal activity. Notably, 4-isopropyl-*N*-propionylthiazoldine-2-thione shows excellent activity against *B. cinerea* and *G. zeae* with IC_{50} values at 3.7 μg/mL and 6.5 μg/mL, respectively, and 4-isobutyl-*N*-propionylthiazoldine-2-thione shows remarkable fungicidal activity against *R. solani*, *S. sclerotiorum*, and *G. zeae* with IC_{50} values at 1.0 μg/mL, 12.1 μg/mL, and 11.0 μg/mL, respectively.



4g

IC_{50} = 3.7 μg/mL for *B.cinerea*
IC_{50} = 6.5 μg/mL for *G.Zeae*



4h

IC_{50} = 1.0 μg/mL for *R. solani*
IC_{50} = 12.1 μg/mL for *S. sclerotiorum*
IC_{50} = 11.0 μg/mL for *G. zeae*

Keywords Thiazolidine-2-thione, Fungicidal, Heterocycle, Synthesis, Bioactivity

INTRODUCTION

Plant pathogenic fungi are one of the main threats for the growth of crops. Developing new fungicides for the control of plant pathogenic fungi is always an imperative demand for the future crops production. Thiazolidines, as the representatives of five-membered heterocycles, are of considerable interest in different areas of medicinal chemistry.[1] As an important class of thiazolidine derivatives, thiazolidine-2-thione derivatives have been widely used in pharmaceuticals and agrochemicals. For example, 1,3-thiazolidine-2,4-diones, Rhodanine derivatives, are well-known compounds which show diversified biological activities such as anti-hyperlycaemics, aldose reductase inhibitors, anti-cancer, anti-inflammatory, anti-arthritics, and anti-microbials.[2] As structural analogs, 1,3-thiazolidine-2-thione derivatives, however, have been seldom reported with their biological activity though they have been widely used as chiral auxiliaries in catalytic asymmetric synthesis in organic chemistry.[3] Previous research has shown that a series of thiazolidine-2-thiones containing *N*-acyl[4] and *N*-arylaminocarbonyl[5] substituents have some fungicidal and pesticide activities. Some *S*-benzylthiazolines, synthesized from thiazolidine-2-thiones, showed moderate or poor activity against *E. subtilis*, *E. coli*, *P. aeruginosa*, *C. albicans*, and *A. niger*.[6] However, all these bioactive compounds were generated from 1,3-thiazolidine-2-thione itself without any substituents on the 4- and/or 5-position(s) in the five-membered ring. Recently, Sasson and Gruzman reported that 2-(benzo[*d*]thiazolin-2-ylmethylthio)-6-ethoxybenzo[*d*]thiazole, an 2-alkylthio substituted thiazoline compound generated from the corresponding benzothiazolidine-2-thione, showed a high fit value to a pharmacophore model derived from the structure of 2-chloro-5-{(*Z*),(*E*)-5-[(5-(4,5-dimethyl-2-

nitrophenyl)furan-2-yl]methylene-4-oxothiazolidin-2-ylideneamino}benzoic acid (PT-1).[7] Their results made us believe that introducing diverse substituents on the thiazolidine-2-thione ring might enhance their various bioactivities. Herein, 32 compounds including 14 new compounds and 20 optically active ones were synthesized and screened for the fungicidal activities against six phytopathogenic fungi with *Rhizoctonia solani*, *Botrytis cinerea*, *Sclerotonia sclerotiorum*, *Gibberella zeae*, *Phytophythora capsici*, and *Alternaria alternate.*

RESULTS AND DISCUSSION

Various 4-alkyl, 4-aryl, 5-alkyl, or 5-aryl-1,3-thiazolidine-2-thiones **2** were synthesized from the corresponding vicinal amino alcohols **1** according to our previous work.[8] Optically active compounds were also generated from the corresponding chiral vicinal amino alcohols. 2-Benzylthio-1,3-thiazolines **3** were generated from **2** and benzyl chloride in good to excellent yields with potassium carbonate as base under reflux.[9]

3-Propionylthiazolidine-2-thiones **4a-c** were synthesized with good yields from **2a-c** and propionyl chloride at room temperature in the presence of triethyl amine (Table 1, entries 9–11).[10] However, the 4-substituted 1,3-thiazolidine-2-thiones **2d** and **2h** gave rise to the corresponding products with lower yields (35% and 27%, respectively) under the same conditions due to steric hindrance (Table 1, entries 12 and 17). In order to improve the yields, we applied the stronger base sodium hydride at −78°C instead of *n*-BuLi used in the literature,[10] and achieved the desired products with good to excellent yields (Table 1, entries 12–16).

N-(4-Chlorophenyl)-2-thioxothiazolidine-3-carboxamides **5** were obtained from 1,3-thiazolidine-2-thiones **2** and *p*-chlorophenyl isocyanate in the presence of triethyl amine at room temperature and subsequent recrystallization from ethanol or a mixture of hexane and diethyl ether. It should be paid attention to the formation of a small amount of ethyl *p*-chlorophenylcarbamate as by-product when ethanol was used as the recrystallization solvent due to alcoholysis.

The preliminary antifungal activities of all synthesized compounds against the phytopathogenic fungi, *Rhizoctonia solani*, *Botrytis cinerea*, *Sclerotonia sclerotiorum*, *Gibberella zeae*, *Phytophythora capsici*, *Alternaria alternata*, were evaluated at a concentration of 25 μg/mL. Their inhibition rates are listed in Table 2. Compared with Azoxystrobin, a commercially available fungicide with a broad spectrum of bioactivity, many compounds shows good to excellent fungicidal activities. 4-Benzylthiazolidine-2-thione (**2f**) and 4-isobutyl-*N*-propionylthiazolidine-2-thione (**4h**) possess high activities against *Sclerotonia sclerotiorum*. In addition, **2f** and 4-isopropyl-*N*-propionylthiazoldine-2-thione (**4g**) also show high antifungal activities against *Botrytis cinerea*. Inspiringly, most *N*-propionyl thiazolidine-2-thiones **4** show moderate to excellent inhibitive activities against the phytopathogenic fungi. Typically, both **4g** and **4h** at 25 μg/mL exhibit a broad fungicidal activity. They especially inhibit the growth of *Gibberella zeae* at 100%, and **4h** at 90% against *Rhizoctonia solani*. In addition, *N*-*p*-chlorophenyl-4-isobutyl-2-thioxothiazolidine-3-carboxamide (**5h**) also shows 90% inhibition to *Rhizoctonia solani*. To analize the structure activity relationship (SARA), the 4-substituted 1,3-thiazolidine-2-thiones **2** show some fungicidal activities against *Sclerotonia sclerotiorum*,

Alternaria alternata, and *Botrytis cinerea*, especially compound **2e**. Comparing with the non-substituted thiazolidine-2-thione **1a**, substituents at the 4- and 5-positions can improve the fungicidal ability, especially 4-substituted compounds, such as **2e** (R^1 = Me), **2f** (R^1 = Bn), and **2h** (R^1 = *i*-Bu). However, all 2-benzylthio-1,3-thiazolines **3** did not show any good fungicidal activity. We are delighted to find that all *N*-propionylthiazolidine-2-thiones **4** displayed moderate to good fungicidal activities, especially 4-substituted ones, such as **4e** (R^1 = Me), **4g** (R^1 = *i*-Pr), and **4h** (R^1 = *i*-Pr). Comparatively, all 4-substituted *N*-*p*-chlorophenyl-2-thioxothiazolidine-3-carboxamides **5** show poor activities, except **5h**. The SARA results demonstrate that *N*-acyl substituents and substituent at the 4-position are preferable for improving the antifungal activity of 1,3-thiazolidine-2-thiones. However, substituents at the 5-position of 1,3-thiazolidine-2-thione and 1,3-thiazoline rings (such as **2b-c**, **3b-c**, **4b-c**, and **5b-c**) are not beneficial for the fungicidal activity.

On the basis of previous bioassays, the IC_{50} values of some excellent fungicidal compounds (**2f**, **4g**, **4h**, and **5h**) are listed in Table 3. Notably, compound **4g** exhibits wonderful activities against *Botrytis cinerea* and *Gibberella zeae* with IC_{50} values of 3.7 and 6.5 μg/mL, and compound **4h** shows excellent antifungal activities with IC_{50} values against *S. sclerotiorum*, *G. zeae*, and *R. solani*, at 12.1 μg/mL, 10.9 μg/mL, and 1.0 μg/mL, respectively.

CONCLUSIONS

In summary, a series of structural simple thiazolidine-2-thione derivatives was synthesized with moderate to good yields and screened for their antifungal activity. A preliminary bioassay shows that all thiazolidine-2-thione derivatives exhibited antifungal activities against *P. capsici*, *G. zeae*, *S. sclerotiorum*, *A. alternate*, *B. cinerea*, or *R. solani*. The SAR analysis reveals that *N*-

acyl substituted and bulky 4-substituents can enhance the antifungal activities. The further antifungal assay demonstrates that two compounds **4g** and **4h** were identified as the most promising candidates for further study. Compound **4g** shows excellent activity against *B. cinerea* and *G. zeae* with IC_{50} values at 3.7 μg/mL and 6.5 μg/mL, respectively, and compound **4h** shows remarkable fungicidal activities against *R. solani*, *S. sclerotiorum*, and *G. zeae* with IC_{50} values from 1.0 to 12.1 μg/mL.

EXPERIMENTAL

Melting points were obtained on a Yanaco MP-500 melting point apparatus and are uncorrected. Optical rotations were measured on a Perkin Elmer 341LC polarimeter or Anton Paar MCP200 polarimeter. The ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 200, Varian Mercury 300 Plus, or Bruker 400 spectrometer with tetramethylsilane (TMS) as internal standard in $CDCl_3$ solution. Chemical shifts (δ) are reported in ppm. IR Spectra ($CDCl_3$) were taken on a Nicolet 5700 Fourier transform infrared (FT-IR) spectrometer. HRMS data were determined using an Agilent LC/MSD TOF mass spectrometer. The Supplemental Materials contains ^{1}H and ^{13}C NMR spectra for selected compounds **3, 4 and 5** (Figures S 1 – S 47)

Supplemental data for this article can be accessed on the publisher's website. <TQ> Please make the words "publisher's website" a live DOI link. </TQ>

General Procedure for the Preparation of 2-Benzylthio-1,3-thiazolines 3

Thiazolidine-2-thione **2** (2.5 mmol), benzyl chloride (317 mg, 2.5 mmol), and K_2CO_3 (691 mg, 5 mmol) were dissolved in 10 mL of acetone. The resulting solution was refluxed for 2-4 h under TLC monitoring and then was allowed to cool to r.t. and filtered. After removal of the solvent, the crude product was obtained and purified by silica-gel column chromatography with a mixture of petroleum ether and EtOAc (10:1, *v/v*) as eluent.

2-Benzylthio-1,3-thiazoline (3a).[6] Yield 89%, colorless crystals. M. p. 50-52°C. ^{1}H NMR (300 MHz): δ 7.46 – 7.24 (m, 5H, ArH), 4.36 (s, 2H, CH_2Ph), 4.23 (t, J = 8.0 Hz, 2H, CH_2N), 3.40 (t, J = 8.0 Hz, 2H, CH_2S). ^{13}C NMR (75 MHz): δ 165.2, 136.5, 129.0, 128.6, 127.5, 64.2, 36.9, 35.6.

(±)-2-Benzylthio-5-methyl-1,3-thiazoline (**3b**).[11] Yield 87%, Pale yellow oil. ^{1}H NMR (300 MHz): δ 7.38-7.26 (m, 5H, ArH), 4.37 (d, J = 13.2 Hz, 1H, CH_2Ph), 4.33 (d, J = 13.2 Hz, 1H, CH_2Ph), 4.19 (dd, J = 6.6, 13.6 Hz, 1H, CH_2N), 4.03 (ddq, J = 4.4, 6.6, 13.2 Hz, 1H, CHS), 3.96 (dd, J = 4.4, 13.6 Hz, 1H, CH_2N), 1.37 (d, J = 6.6 Hz, 1H, CH_3). ^{13}C NMR (75.5 MHz): δ 164.5, 136.5, 129.0, 128.6, 127.4, 71.1, 48.2, 36.8, 21.4.

(*R*)-2-Benzylthio-5-phenyl-1,3-thiazoline (**3c**). Yield 89%, colorless crystals, M.p. 46-49°C. $[\alpha]_D^{20}$ = +298.4 (c = 1.4, Me_2CO). IR: 1561 (C=N). ^{1}H NMR (200 MHz): δ 7.39-7.27 (m, 10H, ArH), 5.03 (dd, J = 8.3, 6.0 Hz, 1H, CHS), 4.52 (dd, J = 14.9, 8.3 Hz, 1H, CH_2N), 4.38 (s, 2H, CH_2Ph), 4.43 (dd, J = 14.9, 6.0 Hz, 1H, CH_2N). ^{13}C NMR (50 MHz): δ 164.4, 141.0, 136.4, 129.0, 128.7, 128.5, 127.8, 127.4, 127.0, 72.1, 56.7, 36.8. HRMS (ESI) *m/z* 286.0712. Calcd for $C_{16}H_{16}NS_2^+$: 286.0719 $[M+H]^+$.

(*S*)-2-Benzylthio-4-phenyl-1,3-thiazoline (**3d**). Yield 92%. M. p. 59-60°C. $[\alpha]_D^{20}$ = +170.2 (*c* = 1.4, Me_2CO). IR: 1566 (C=N). ^{1}H NMR (300 MHz): δ 7.31 (m, 10H, ArH), 5.49 (dd, *J* = 8.3, 9.0 Hz, 1H, CHN), 4.45 (d, *J* = 13.2 Hz, 1H, CH_2Ph), 4.36 (d, *J* = 13.2 Hz, 1H, CH_2Ph), 3.75 (dd, *J* = 8.3, 10.8 Hz, 1H, CH_2S), 3.26 (dd, *J* = 9.0, 10.8 Hz, 1H in CH_2S). ^{13}C NMR (75.5 MHz): δ 165.6, 141.5, 136.7, 129.1, 128.55, 128.50, 127.6, 127.4, 126.4, 79.5, 42.9, 37.0. HRMS (ESI) *m/z*, 286.0714. Calcd. for $C_{16}H_{16}NS_2$: 286.0719 $[M+H]^+$.

(*S*)-2-Benzylthio-4-benzyl-1,3-thiazoline (**3f**). Yield 91%. Pale yellow oil. $[\alpha]_D^{20}$ = –34.0 (*c* = 0.6, Me_2CO). IR: 1564 (C=N). ^{1}H NMR (300 MHz): δ 7.37–7.14 (m, 10H, ArH), 4.67 (dddd, *J* = 8.7, 7.8, 6.7, 5.4 Hz, 1H, CHN), 4.38 (d, *J* = 13.2 Hz, 1H, CH_2Ph), 4.29 (d, *J* = 13.2 Hz, 1H, CH_2Ph), 3.27 (dd, *J* = 10.9, 7.8 Hz, 1H, CH_2S), 3.14 (dd, *J* = 13.6, 5.4 Hz, 1H, CH_2Ph), 3.09 (dd, *J* = 10.9, 6.7 Hz, 1H, CH_2S), 2.73 (dd, *J* = 13.6, 8.7 Hz, 1H, CH_2Ph). ^{13}C NMR (75 MHz): δ 164.15, 138.34, 136.67, 129.17, 128.96, 128.40, 127.32, 126.38, 77.62, 39.98, 39.10, 36.86. HRMS (ESI) *m/z* 300.0878. Calcd. for $C_{17}H_{18}NS_2^+$: 300.0875 $[M+H]^+$.

(*S*)-2-Benzylthio-4-isopropyl-1,3-thiazoline (**3g**). Yield 90%. Pale yellow oil. $[\alpha]_D^{20}$ = –6.3 (*c* = 0.7, Me_2CO). IR: 1564 (C=N). ^{1}H NMR (300 MHz): δ 7.37-7.20 (m, 5H, ArH), 4.36 (d, *J* = 13.2 Hz, 1H, CH_2Ph), 4.36 (d, *J* = 13.2 Hz, 1H, CH_2Ph), 4.16 (ddd, *J* = 9.8, 8.4, 6.6 Hz, 1H, CHN), 3.34 (dd, *J* = 10.2, 8.4 Hz, 1H in CH_2S), 3.10 (dd, *J* = 10.2, 9.8 Hz, 1H in CH_2S), 1.94 (dhept, *J* = 6.6, 6.6 Hz, 1H, CH in *i*Pr), 1.04 (d, *J* = 6.6 Hz, 3H, CH_3), 0.96 (d, *J* = 6.6 Hz, 3H, CH_3). ^{13}C NMR (75 MHz): δ 162.4, 137.1, 129.0, 128.4, 127.2, 83.1, 37.5, 36.8, 33.1, 19.7, 19.1. HRMS (ESI) *m/z* 252.0872. Calcd. for $C_{13}H_{18}NS_2^+$: 252.0875 $[M+H]^+$.

(*S*)-2-Benzylthio-4-isobutyl-1,3-thiazoline (**3h**). Yield 91%. Pale yellow oil. $[\alpha]_D^{20}$ = –32.9 (*c* = 0.8, Me_2CO). IR: 1567 (C=N). ^{1}H NMR (300 MHz): δ 7.37-7.21 (m, 5H, ArH), 4.46 (m,

1H, CHN), 4.35 (d, *J* = 13.2 Hz, 1H, CH_2Ph), 4.30 (d, *J* = 13.2 Hz, 1H, CH_2Ph), 3.44 (dd, *J* = 10.6, 7.8 Hz, 1H, CH_2S), 3.01 (dd, *J* = 10.6, 7.9 Hz, 1H, CH_2Ph), 1.83 (dt, *J* = 13.3, 6.6, 1H, CH_2 at *i*Bu), 1.69 (ddhept, *J* = 6.6, 6.6, 6.6 Hz, 1H, CH, *i*Bu), 1.38 (dt, *J* = 13.7, 7.0 Hz, 1H, CH_2 at *i*Bu), 0.99 (d, *J* = 6.6 Hz, 3H, CH_3), 0.96 (d, *J* = 6.6 Hz, 3H, CH_3). ^{13}C NMR (75 MHz): δ 162.7, 136.9, 129.0, 128.4, 127.3, 75.1, 44.0, 40.4, 36.9, 25.9, 22.71, 22.65. HRMS (ESI) *m/z* 266.1038. Calcd. for $C_{14}H_{20}NS_2^+$: 266.1032 $[M+H]^+$.

General Procedure for the Preparation of 3-Propionyl-thioazolidine-2-thiones 4

Under N_2 atmosphere, NaH (120 mg, 60% dispersion in mineral oil, 3 mmol) was added to a solution of thiazolidine-2-thione **2** (2.5 mmol) in 5 mL of THF and the resulting solution was cooled to −78°C by a dry-ice-acetone bath. Propionyl chloride (255 mg, 2.5 mmol, 480 µL) was then dropped in. After removal of the solvent in vacuo, the residue was purified by column chromatography with a mixture of petroleum ether (60-90°C)/EtOAc (5:1, *v/v*) as eluent.

***N*-Propionyl-thiazolidine-2-thione** (**4a**).[10] Yield 98%, yellow crystals. M.p. 47-48°C. ^{1}H NMR (300 MHz): δ 4.60 (t, *J* = 7.5 Hz, 2H, CH_2N), 3.30 (t, *J* = 7.5 Hz, 2H, CH_2S), 3.26 (d, *J* = 7.2 Hz, 2H, CH_2), 1.18 (t, *J* = 7.2, 3H, CH_3). ^{13}C NMR (75 MHz): δ 201.5, 175.5, 56.0, 32.2, 28.3, 8.7.

(±)-5-Methyl-*N*-propionyl-thiazolidine-2-thione (**4b**). Yield, 90%, yellow crystals. M. p. 107-108°C (*n*-hexane/EtOAc). IR: 1701 (C=O), 1163 (C=S). ^{1}H NMR (200 MHz): δ 4.62 (dd, *J* = 12.2, 7.1 Hz, 1H, CH_2N), 4.24 (dd, *J* = 12.2, 6.4 Hz, 1H, CH_2N), 3.78 (ddq, J = 7.1, 6.4, 6.7 Hz, 1H, CHS), 3.27 (q, *J* = 7.2 Hz, 2H, CH_2), 1.47 (d, *J* = 6.7 Hz, 3H, CH_3), 1.18 (t, *J* = 7.2 Hz,

3H, CH_3). ^{13}C NMR (50 MHz): δ 201.4, 175.7, 62.4, 39.0, 32.3, 19.5, 8.8. HRMS (ESI) *m/z* 190.0350. Calcd for $C_7H_{12}NOS_2^+$: 190.0355 $[M+H]^+$.

(*S*)-5-Phenyl-*N*-propionyl-thiazolidine-2-thione (**4c**). Yield 95%, yellow oil. $[\alpha]_D^{20}$ = +271.4 (c = 0.9, Me_2CO). IR: 1699 (C=O), 1174 (C=S). ^1H NMR (300 MHz): δ 7.44-7.30 (m, 5H, ArH), 4.91 (dd, *J* = 7.6, 3.0 Hz, 1H, CH_2S), 4.87 (dd, *J* = 7.6, 1.4 Hz, 1H), 4.57 (dd, *J* = 15.0, 10.6 Hz, 1H, CHS), 3.33 (dq, *J* = 18.1, 7.2 Hz, 1H, CH_2CO), 3.24 (dq, *J* = 18.1, 7.2 Hz, 1H, CH_2CO), 1.19 (t, *J* = 7.2, 3H). ^{13}C NMR (75 MHz): δ 200.7, 175.4, 136.6, 129.2, 128.7, 127.3, 62.6, 47.9, 32.3, 8.8. HRMS (ESI) *m/z* 252.0517. Calcd for $C_{12}H_{14}NOS_2^+$: 252.0511 $[M+H]^+$.

(*S*)-*N*-Propionyl-4-phenyl-thiazolidine-2-thione (4d).[10] Yield 98%, sticky yellow oil. $[\alpha]_D^{20}$ = +289.9 (c. 0.8, Me_2CO). ^1H NMR (300 MHz): δ 7.43-7.28 (m, 5H, ArH), 6.25 (dd, *J* = 1.5, 8.2 Hz, 1H, CHN), 3.94 (dd, *J* = 8.2, 11.2 Hz, 1H, CH_2S), 3.38 (dq, *J* = 18.2, 7.2 Hz, 1H, CH_2CO), 3.20 (dq, *J* = 18.2, 7.2 Hz, 1H, CH_2CO), 3.08 (dd, *J* = 1.5, 11.2 Hz, 1H, CH_2S), 1.13 (t, *J* = 7.2 Hz, 3H, CH_3). ^{13}C NMR (75 MHz) δ: 202.1, 174.7, 139.2, 129.0, 128.4, 125.4, 69.8, 36.6, 32.5, 8.7.

(*S*)-4-Methyl-*N*-propionyl-thiazolidine-2-thione (**4e**). Yield: 98%. Sticky yellow oil. $[\alpha]_D^{20}$ = +258.0 (*c* = 1.2, Me_2CO). IR: 1697 (C=O), 1173 (C=S). ^1H NMR (300 MHz): δ 5.34 (ddd, *J* = 7.3, 6.4, 0.9, 1H, CHN), 3.64 (dd, *J* = 11.2, 7.4 Hz, 1H, CH_2S), 3.37 (dq, *J* = 18.0, 7.3 Hz, 1H, CH_2CO), 3.09 (dq, *J* = 18.0, 7.2 Hz, 1H, CH_2CO), 2.80 (dd, *J* = 11.2, 0.9 Hz, 1H, CH_2S), 1.51 (d, *J* = 6.4 Hz, 3H, CH_3), 1.17 (t, *J* = 7.2 Hz, 3H, CH_3). ^{13}C NMR (50 MHz): δ 200.8, 174.8, 63.5, 35.5, 32.2, 18.1, 8.7. HRMS (ESI) *m/z*, 190.0350, Calcd. for $C_7H_{12}NOS_2^+$: 190.0355 $[M+H]^+$.

(*S*)-4-Benzyl-*N*-propionyl-thiazolidine-2-thione (4f).[10] Yield 98%, yellow crystals, M. p. 112-113°C (*n*-hexane/EtOAc). $[\alpha]_D^{20}$ = +184.2 (c. 1.3, Me_2CO). ^{1}H NMR (300 MHz): δ 7.38 – 7.22 (m, 5H, ArH), 5.38 (ddd, *J* = 10.5, 7.2, 3.9, 1H, CHN), 3.42 (dq, *J* = 18.2, 7.2 Hz, 1H, CH_2CO), 3.38 (ddd, *J* = 11.5, 7.2, 1.6 Hz, 1H, CH_2Ph), 3.21 (dd, *J* = 13.1, 3.9 Hz, 1H, CH_2S), 3.11 (dq, *J* = 18.2, 7.2 Hz, 1H, CH_2CO), 3.04(d, *J* = 13.1, 10.5 Hz, 1H, CH_2S), 2.87 (d, *J* = 11.6 Hz, 1H, CH_2Ph), 1.19 (t, *J* = 7.2 Hz, 3H, CH_3). ^{13}C NMR (50 MHz): δ 201.0, 174.8, 136.5, 129.4, 128.8, 127.1, 68.6, 36.7, 32.3, 31.9, 8.8.

(*S*)-4-Isopropyl-*N*-propionyl -thiazolidine-2-thione (4g).[10] Yield 96%, sticky yellow oil, $[\alpha]_D^{20}$ = +409.1 (c. 1.2, Me_2CO). ^{1}H NMR (300 MHz): δ 5.17 (ddd, *J* = 8.1, 6.4, 1.3 Hz, 1H, CHN), 3.52 (dd, *J* = 11.5, 8.1 Hz, 1H, CH_2S), 3.36 (dq, *J* = 18.0, 7.2 Hz, 1H, CH_2CO), 3.15 (dq, *J* = 18.0, 7.2 Hz, 1H, CH_2CO), 3.03 (dd, *J* = 11.5, 1.3 Hz, 1H, CH_2S), 2.37 (dhept, *J* = 6.3, 6.9 Hz, 1H, CH), 1.17 (t, *J* = 7.2 Hz, 3H, CH_3), 1.06 (d, *J* = 6.9 Hz, 3H, CH_3), 0.98 (d, *J* = 6.9 Hz, 3H, CH_3). ^{13}C NMR (50 MHz): δ 202.6, 174.8, 71.6, 32.0, 30.7, 30.4, 19.0, 17.6, 8.9.

(*S*)-4-Isobutyl-*N*-propionyl-thiazolidine-2-thione (**4h**).[10] Yield 66%, sticky yellow oil. ^{1}H NMR (300 MHz): δ 5.29 (ddd, *J* = 10.3, 7.2, 3.4 Hz, 1H, CHN), 3.56 (ddd, *J* = 11.3, 7.2, 1.1 Hz, 1H, CH_2S), 3.37 (dq, *J* = 18.2, 7.2 Hz, 1H, CH_2CO), 3.10 (dq, *J* = 18.2, 7.2 Hz, 1H, CH_2CO), 2.91 (d, *J* = 11.3 Hz, 1H, CH_2S), 1.93 (ddd, *J* = 13.2, 10.3, 3.9 Hz, 1H, CH_2), 1.66 (ddhept, *J* = 9.8, 3.9, 6.4 Hz, 1H, CH), 1.55 (dddd, *J* = 13.2, 9.8, 3.4, 1.1 Hz, 1H, CH_2), 1.17 (t, *J* = 7.2, 3H, CH_3), 1.01 (d, *J* = 6.4 Hz, 3H, CH_3), 1.00 (d, *J* = 6.4 Hz, 3H, CH_3). ^{13}C NMR (50 MHz): δ 201.4, 174.7, 66.1, 39.6, 33.0, 32.2, 25.4, 23.5, 21.3, 8.8.

General Procedure for the Preparation of *N*-(4-Chlorophenyl)-2-thioxothiazolidine-3-carboxamides 5

To a solution of thiazolidine-2-thione (2 mmol) in 10 mL of anhydrous THF was added anhydrous Et_3N (202 mg, 2 mmol, 278 μL) and *p*-chlorophenylisocyanoate (306 mg, 2 mmol). The resulting solution was stirred for 0.5~2 h under TLC monitoring. After removal of the solvent in vacuo, the white solid was collected and further purified *via* recrystallization from EtOH or a mixture of hexanes and diethyl ether, or by column chromatography with a mixture of petroleum ether (60-90°C)/EtOAc (5:1, *v/v*) as eluent.

***N*-(4-Chlorophenyl)-2-thioxothiazolidine-3-carboxamide (5a)**.[5] Yield 99%, colorless crystals. M. p. 137-138°C (EtOH). ^{1}H NMR (200 MHz): δ 12.12 (br s, 1H, NH), 7.46 (d, J = 8.9 Hz, 2H, ArH), 7.29 (d, J = 8.9 Hz, 2H, ArH), 4.77 (t, J = 7.9 Hz, 2H, CH_2N), 3.30 (t, J = 7.8 Hz, 2H, CH_2N). ^{13}C NMR (50 MHz): δ 200.9, 149.5, 135.5, 129.7, 129.1, 121.5, 56.1, 26.7.

(±)-*N*-(4-Chlorophenyl)-4-methyl-2-thioxothiazolidine-3-carboxamide (**5b**). Yield 92%, colorless crystals. M. p. 143–144°C (EtOH). IR: 1711(C=O). ^{1}H NMR (300 MHz): δ 12.14 (br s, 1H, NH), 7.46 (d, J = 8.8 Hz, 2H, ArH), 7.29 (d, J = 8.8 Hz, 2H, ArH), 4.76 (dd, J = 12.3, 7.3 Hz, 1H, CH_2N), 4.44 (dd, J = 12.3, 6.0 Hz, 1H, CH_2N), 3.92 – 3.63 (ddq, J = 7.3, 6.0, 6.8 Hz, 1H, CHS), 1.51 (d, J = 6.8 Hz, 3H, CH_3). ^{13}C NMR (75 MHz): δ 200.6, 149.6, 135.5, 129.6, 129.0, 121.5, 62.5, 37.6, 19.9. HRMS (ESI) *m/z*, 287.0078. Calcd. for $C_{11}H_{12}ClN_2OS_2^+$: 287.0074 $[M+H]^+$.

(*R*)-*N*-(4-Chlorophenyl)-5-phenyl-2-thioxothiazolidine-3-carboxamide (**5c**). Yield 95%, colorless crystals. M. p. 121–122°C (diethyl ether). $[\alpha]_D^{20}$ = +238.5 (c = 1.3, Me_2CO). IR: 1712 (C=O). ^{1}H NMR (300 MHz): δ 12.15 (br s, 1H, NH), 7.47 (d, J = 8.8 Hz, 2H, ArH), 7.39-

7.31(m, 5H, ArH), 7.30 (d, *J* = 8.8 Hz, 2H, ArH), 5.06 (dd, *J* = 11.8, 7.4 Hz, 1H, CH_2N), 4.88 (dd, *J* = 7.4, 7.4 Hz, 1H, CHS), 4.79 (dd, *J* = 11.8, 7.4 Hz, 1H, CH_2N). ^{13}C NMR (50 MHz): δ 200.0, 149.4, 136.7, 135.4, 129.8, 129.3, 129.1, 129.0, 127.3, 121.5, 62.7, 46.3. HRMS (ESI) *m/z*, 349.0230. Calcd. for $C_{16}H_{14}ClN_2OS_2^+$: 349.0231 $[M+H]^+$.

(*S*)-*N*-(4-Chlorophenyl)-4-phenyl-2-thioxothiazolidine-3-carboxamide (**5d**). Yield 91%, colorless crystals. M. p. 136–137°C (EtOH). $[\alpha]_D^{20}$ = +489.7 (*c* = 0.7, Me_2CO). IR: 1710 (C=O). ^1H NMR (300 MHz): δ 12.25 (br s, 1H, NH), 7.43-7.26 (m, 8H, ArH), 7.24 (d, *J* = 8.7 Hz, 2H, ArH, AA'BB' system), 6.48 (d, *J* = 8.7, 1.0 Hz, 1H, CHN), 3.96 (dd, *J* = 11.2, 8.7 Hz, 1H, CH_2S), 3.03 (dd, *J* = 11.2, 1.0 Hz, 1H, CH_2S). ^{13}C NMR (75 MHz): δ 201.3, 148.8, 138.9, 135.4, 129.6, 129.1, 129.0, 128.7, 125.3, 121.4, 69.9, 35.0. HRMS (ESI) *m/z*, 349.0233. Calcd. for $C_{16}H_{14}ClN_2OS_2^+$: 349.0231 $[M+H]^+$.

(*S*)-*N*-(4-Chlorophenyl)-4-methyl-2-thioxothiazolidine-3-carboxamide (**5e**). Yield 96%, colorless crystals. M. p. 108–110°C (*n*-hexane/EtOAc). $[\alpha]_D^{20}$ = +89.0 (*c* = 0.9, Me_2CO). IR: 1710 (C=O). ^1H NMR (300 MHz): δ 12.21 (s, 1H, NH), 7.47 (d, *J* = 8.9 Hz, 2H, ArH), 7.30 (d, *J* = 8.9 Hz, 2H, ArH), 5.58 (ddq, *J* = 7.8, 0.6, 6.4 Hz, 1H, CHN), 3.68 (dd, *J* = 11.2, 7.8 Hz, 1H, CH_2S), 2.80 (dd, *J* = 11.2, 0.6 Hz, 1H, CH_2S), 1.58 (d, *J* = 6.4, 3H, CH_3). ^{13}C NMR (75 MHz): δ 199.8, 149.0, 135.5, 129.6, 129.0, 121.5, 63.8, 33.9, 18.4. HRMS (ESI) *m/z*, 287.0072 Calcd. for $C_{11}H_{12}ClN_2OS_2^+$: 287.0074 $[M+H]^+$.

(*S*)-4-Benzyl-*N*-(4-chlorophenyl)-2-thioxothiazolidine-3-carboxamide (**5f**). Yield 72%, colorless crystals. M. p. 131–132°C (CH_2Cl_2). $[\alpha]_D^{20}$ = +91.5 (*c* = 0.9, Me_2CO). IR: 1707 (C=O). ^1H NMR (300 MHz): δ 12.25 (s, 1H, NH), 7.48 (d, *J* = 8.9 Hz, 2H, ArH), 7.32 (m, 7H, ArH), 5.61 (ddd, *J* = 10.7, 7.3, 3.7 Hz, 1H, CHN), 3.43 (ddd, *J* = 11.6, 7.7, 0.8 Hz, 1H, CH_2Ph),

3.30 (dd, *J* = 13.1, 3.6 Hz, 1H, CH_2S), 3.09 (dd, *J* = 13.1, 10.5 Hz, 1H, CH_2S), 2.89 (d, *J* = 11.6 Hz, 1H, CH_2Ph). ^{13}C NMR (75 MHz): δ 200.5 149.3, 136.2, 135.5, 129.8, 129.4, 129.1, 128.9, 127.3, 121.7, 68.9, 36.9, 30.4. HRMS (ESI) *m/z*, 363.0381, Calcd. for $C_{17}H_{16}ClN_2OS_2^+$: 363.0387 $[M+H]^+$.

(*S*)-*N*-(4-Chlorophenyl)-4-isopropyl-2-thioxothiazolidine-3-carboxamide (**5g**). Yield 80%, colorless crystals. M. p. 118–120°C (EtOH). $[\alpha]_D^{20}$ = +262.1 (*c* = 0.7, Me_2CO). IR: 1709 (C=O). ^1H NMR (300 MHz): δ 12.28 (br s, 1H, NH), 7.47 (d, *J* = 8.9 Hz, 2H, ArH), 7.30 (d, *J* = 8.9 Hz, 2H, ArH), 5.40 (ddd, *J* = 8.8, 5.4, 1.2, 1H, CHN), 3.56 (dd, *J* = 11.5, 8.8 Hz, 1H, CH_2S), 3.00 (dd, *J* = 11.5, 1.2 Hz, 1H, CH_2S), 2.63–2.22 (dhept, *J* = 5.4, 6.9 Hz, 1H, CH), 1.08 (d, *J* = 6.9 Hz, 3H, CH_3), 1.03 (d, *J* = 6.9 Hz, 3H, CH_3). ^{13}C NMR (75 MHz): δ 201.2, 149.4, 135.6, 129.6, 129.0, 121.5, 72.2, 31.2, 28.2, 18.9, 17.2. HRMS (ESI) *m/z*, 315.0383, Calcd. for $C_{13}H_{16}ClN_2OS_2^+$: 315.0387 $[M+H]^+$.

(*S*)-*N*-(4-Chlorophenyl)-4-isobutyl-2-thioxothiazolidine-3-carboxamide (**5h**). Yield 90%, colorless crystals. M. p. 106–108°C (EtOH). $[\alpha]_D^{20}$ = +116.6 (*c* = 1.0, Me_2CO). IR: 1710 (C=O). ^1H NMR (300 MHz): δ 12.22 (br s, 1H, NH), 7.46 (d, *J* = 8.9 Hz, 2H, ArH), 7.29 (d, *J* = 8.9 Hz, 2H, ArH), 5.56 – 5.45 (m, 1H, CHN), 3.60 (dd, *J* = 11.3, 7.7 Hz, 1H, CH_2S), 2.92 (d, *J* = 11.3 Hz, 1H, CH_2S), 2.01-1.94 (m, 1H, CH_2), 1.74 – 1.60 (m, 2H, CH and 1H, CH_2 at *i*Bu), 1.03 (d, *J* = 6.2 Hz, 3H, CH_3). 1.01 (d, J = 6.2 Hz, 3H, CH_3). ^{13}C NMR (75 MHz): δ 200.2, 149.1, 135.5, 129.6, 129.0, 121.6, 66.5, 39.7, 31.5, 25.5, 23.6, 21.2. HRMS (ESI) *m/z*, 329.0549, Calcd. for $C_{14}H_{18}ClN_2OS_2^+$: 329.0544 $[M+H]^+$.

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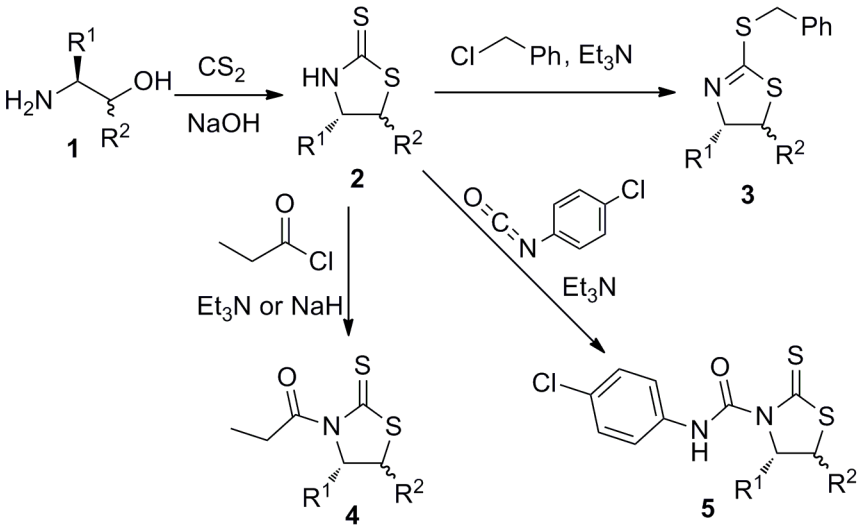


a: $R^1 = R^2 = H$; **b**: $R^1 = H$, $R^2 = Me$;
c: $R^1 = H$, $R^2 = (R)$-Ph; **d**: $R^1 = (S)$-Ph, $R^2 = H$;
e: $R^1 = (S)$-Me, $R^2 = H$; **f**: $R^1 = (S)$-Bn, $R^2 = H$;
g: $R^1 = (S)$-*i*-Pr, $R^2 = H$; **h**: $R^1 = (S)$-*i*-Bu, $R^2 = H$

Scheme 1 Synthesis of thiazolidine-2-thione derivatives

Table 1 Physical and analytical data of **3a**–**5h**.

Entry	Compd.	Yield/%[a]	M.p./°C	Specific Rotation
1	**3a**	89	50–52	–
2	**3b**	87	oil	–
3	**3c**	89	46–49	+298.4 (c. 1.4, Me_2CO)
4	**3d**	92	59–60	+170.2 (c. 0.9, Me_2CO)
5	**3e**	92	oil	–55.2 (c. 1.1, Me_2CO)
6	**3f**	91	oil	–34.0 (c. 0.6, Me_2CO)
7	**3g**	90	oil	–6.3 (c. 0.7, Me_2CO)
8	**3h**	94	oil	–32.9 (c. 0.8, Me_2CO)
9	**4a**	98[b]	47–48	–
10	**4b**	90[b]	107–108	–
11	**4c**	95[b]	oil	+271.4 (c. 0.9, Me_2CO)
12	**4d**	25[b]	oil	+289.9 (c. 0.8, Me_2CO)
13		98[c]		
14	**4e**	98[c]	oil	+258.0 (c. 1.2, Me_2CO)
15	**4f**	98[c]	112-113	+184.2 (c. 1.3, Me_2CO)

16	**4g**	96 [c]	oil	+409.1 (c. 1.2, Me_2CO)
17	**4h**	27 [b]	oil	+292.9 (c. 1.3, Me_2CO)
18		66 [c]		
19	**5a**	99	137–138	–
20	**5b**	92	143–144	–
21	**5c**	95	121–122	+238.5 (c. 1.3, Me_2CO)
22	**5d**	91	136–137	+489.7 (c. 0.7, Me_2CO)
23	**5e**	96	108–110	+89.0 (c. 0.9, Me_2CO)
24	**5f**	72	131–132	+91.5 (c. 0.9, Me_2CO)
25	**5g**	80	118–120	+262.1 (c. 0.7, Me_2CO)
26	**5h**	90	106–108	+116.6 (c. 1.0, Me_2CO)

[a] Isolated yield generated from **2**. [b] Yield from Et_3N as the base. [c] Yield from NaH as the base.

Table 2. Fungicidal activities of all synthesized compounds **2a**–**5h** at concentrations of 25 μg/mL.

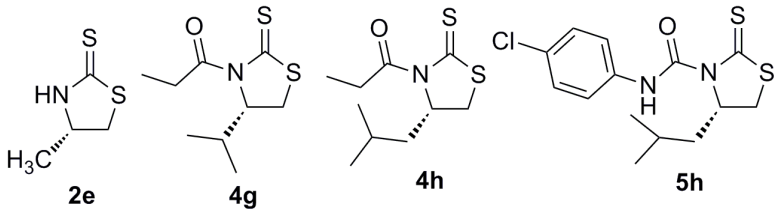
Entry	Compd	Inhibition rate [a](%)					
		P. C.	*G. Z.*	*S. S*	*A. A.*	*B. C.*	*R. S.*
1	**2a**	0	0	0	13.79	20.41	0
2	**2b**	0	0	67.57	17.24	20.41	80.0
3	**2c**	0	0	0	55.17	51.02	0
4	**2d**	0	0	40.54	44.83	85.71	0
5	**2e**	0	0	90.54	37.93	100	80.0
6	**2f**	0	0	89.19	48.28	57.14	0
7	**2g**	0	0	27.03	31.03	10.2	0
8	**2h**	0	0	87.84	44.83	30.61	0
9	**3a**	14.29	36.36	0	24.14	36.73	0
10	**3b**	21.43	40.91	0	20.69	40.82	0

11	**3c**	0	31.82	75.68	34.48	46.94	80.0
12	**3d**	0	38.64	27.03	27.59	44.90	0
13	**3e**	21.43	34.09	0	17.24	26.53	0
14	**3f**	3.57	11.36	75.68	31.03	16.33	0
15	**3g**	0	22.73	0	41.38	36.73	0
16	**3h**	0	38.64	0	24.14	40.82	0
17	**4a**	17.86	25.00	0	24.14	36.73	0
18	**4b**	25	20.45	0	34.48	46.94	0
19	**4c**	10.71	34.09	47.30	51.72	81.63	0
20	**4d**	32.14	54.55	40.54	55.17	55.10	0
21	**4e**	89.29	97.73	67.57	48.28	87.76	0
22	**4f**	7.14	54.55	27.03	48.28	30.61	0
23	**4g**	78.57	100	77.03	48.28	95.92	80.0
24	**4h**	32.14	100	97.3	44.83	71.43	90.0
25	**5a**	0	18.18	0	10.34	6.12	0
26	**5b**	0	11.36	0	17.24	10.20	0
27	**5c**	0	9.09	33.78	27.59	51.02	0
28	**5d**	0	6.82	70.27	31.03	20.41	0

29	**5e**	0	18.18	0	31.03	30.61	0
30	**5f**	0	20.45	60.81	34.48	30.61	0
31	**5g**	0	15.91	0	20.69	30.61	0
32	**5h**	0	27.27	0	13.79	28.57	90.0
33	*Azo*[b]	42.86	81.82	64.86	55.17	42.86	30.0

[a] *RS, Rhizoctonia solani*; *BC, Botrytis cinerea*; *SS, Sclerotonia sclerotiorum*; *GZ, Gibberella zeae*; *PC, Phytophythora capsici*; and *AA, Alternaria alternate.* [b]*Azo, abbr. for azoxystrobin.*

Table 3. *In-vitro* IC_{50} values of **2e**, **4g**, **4h**, and **5h**.



Entry	Compd.	Phytopathogenic fungi	IC_{50} (μg/mL)
1	**2e**	*Botrytis cinerea*	16.51
2	**2e**	*Sclerotonia sclerotiorum*	20.02
3	**4g**	*Botrytis cinerea*	3.75
4	**4g**	*Gibberella zeae*	6.51
5	**4h**	*Sclerotonia sclerotiorum*	12.10
6	**4h**	*Gibberella zeae*	10.97
7	**4h**	*Rhizoctonia solani*	1.01
8	**5h**	*Rhizoctonia solani*	20.41