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2-(4-Oxo-1,3-thiazolidin-2-ylidene)acetamid as promising scaffold for designing new antifungal compounds

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Abstract

1,3-Thiazolidin-4-one derivatives with an exocyclic C=C double bond in position 2 of the hetero ring have a wide spectrum of biological activity, but their fungicidal activity has not been studied as much as it should be. This paper presents a simple and convenient approach for obtaining potential antifungal agents based on 2-(4-oxo-1,3-thiazolidin-2-ylidene)acetamides. The first examples of evaluating the fungicidal activity of 8 obtained compounds on 8 strains of phytopathogenic fungi are presented. A highly active compound **4e** with EC_{50} of 0.85 and 2.29 μg/mL against *A. solani* and *P. lingam*, respectively, was found to be promising for further study.

Keywords

1,3-thiazolidine
cyanoacetamide
exocyclic double bond
fungicide
biological activity

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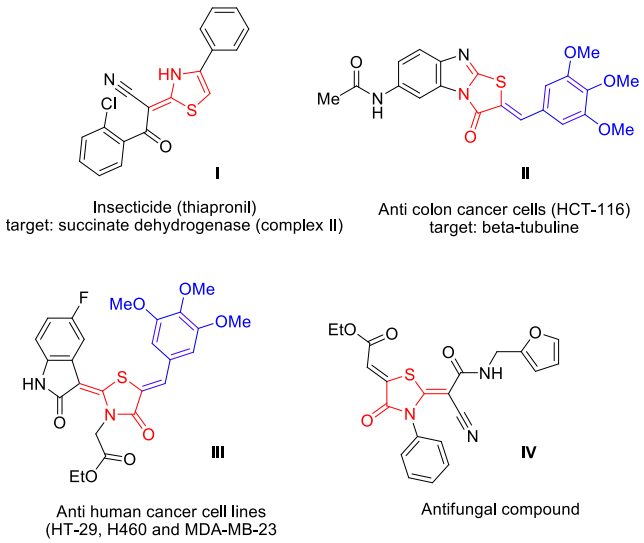
Supplementary materials

1. Introduction

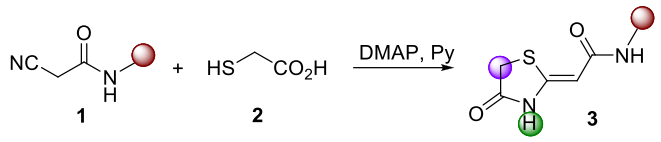
Derivatives of 1,3-thiazolidin-4-one with a double C=O, C=N, C=S, C=C exocyclic bond in position 2 of the hetero ring have a wide range of biological activity: antituberculosis [1], antioxidant [2], anticancer [3, 4], antiinflammatory [5], anticonvulsant [6], antiviral [7, 8], trypanocidal [9], antiarrhythmic [10], antibacterial [11, 12] and fungicidal [12, 13]. Although 1,3-thiazolidines and 1,3-thiazolines have centers for polar interactions and hydrogen bonds [14], these heterocycles often act as a scaffold for substituents interacting with biotargets. Thus, the analysis of the crystal structure of the complex of succinate dehydrogenase with the inhibitor thiapronil **I** (pdb id: 6MYR) showed that thiapronil **I** does not form strong non-covalent interactions (hydrogen bonds and π–π interactions) with the enzyme due to the 1,3-thiazol-2-ylidene fragment [15]. Anticancer compounds **II** [16] and **III** [17] containing a 3,4,5-trimethoxyphenyl substituent are prominent examples as well. Due to this substituting group, compounds **II** and **III** bind to the bioreceptor tubulin (Scheme 1) [18].

It is known that 1,3-thiazolidine derivatives with C=O [2, 19], C=N [20–22], C=S [23] exocyclic bonds in position 2 of the hetero ring show fungicidal properties. However, information on the study of the antifungal properties of 1,3-thiazolidine with a C=C double bond in position 2 of the ring is limited [12]. For example, 1,3-thiazolidin-2-ylidene **IV** is known to exhibit antifungal activity against human pathogens *C. albicans* and *C. neoformans* [24].

One of the convenient methods for the synthesis of 1,3-thiazolidin-2-ylidene derivatives is the condensation of cyanoacetamides **1** with thioglycolic acid **2** (Scheme 2) [25]. In this case, 1,3-thiazolidin-2-ylidenes **3** can be modified both at the NH and CH_2 groups of the hetero ring.



Scheme 1 Examples of active 1,3-thiazol-2-ylidene and 1,3-thiazolidin-2-ylidene derivatives.



Scheme 2 Synthesis of 1,3-thiazolidin-2-ylidenes.

As a result of varying the substituents in the acetamide fragment and the hetero ring, a wide range of 1,3-thiazolidin-2-ylidenes can be obtained for the search for biologically active compounds.

In this paper, we present the first results of using this approach to search for antifungal compounds.

2. Experimental

2.1. Synthesis of target compounds

^{1}H and ^{13}C NMR spectra were recorded with a Bruker Avance II (Karlsruhe, Germany) spectrometer (400 MHz for ^{1}H, 100 MHz for ^{13}C) using Me_4Si as an internal standard. The NMR spectra of all compounds are demonstrated in the Supporting Information (Figures S1–S10). Mass spectra were recorded with a Shimadzu GCMS-QP 2010 "Ultra" (Kyoto, Japan) in electron ionization (EI) mode (electron energy 70 eV). The Fourier transform infrared (FT-IR) spectra were obtained using a Bruker Alpha (ATR, ZnSe) spectrometer (Ettlingen, Germany). Elemental analyses were performed with a Perkin-Elmer 2400 Series II CHNS/O analyzer (Shelton, CT USA). Melting points were determined using a Stuart SMP 3 apparatus (Staffordshire, ST15 OSA, UK). The progress of the reactions and the purity of the compounds were monitored by thin-layer chromatography (TLC, Merck KGaA) in an ethyl acetate-hexane system.

The synthesis of compounds **3a–c** was carried out according to the published method [25].

Alkylation reaction of thiazolidines **3a–c** with the formation of products **4a–e** was carried out according to the published method [26].

(2Z)-*N*-benzyl-2-(4-oxo-1,3-thiazolidin-2-ylidene)acetamide (3a). Yield 0.37 g (72%), white powder, mp 207–209 °C (lit. 208–209 °C [25]).

(2Z)-2-(4-oxo-1,3-thiazolidin-2-ylidene)-*N*-phenylacetamide (3b). Yield 0.44 g (67%), white powder, mp 290–293 °C (decomp.) (lit. 282–285 °C [25]).

(2Z)-*N*-(2-methylphenyl)-2-(4-oxo-1,3-thiazolidin-2-ylidene)acetamide (3c). Yield 0.23 g (75%), white powder, mp 235–236 °C. IR spectrum, ν, cm^{-1}: 3205 (NH), 2969, 2594, 1702 (C=O), 1623 (C=O), 1600, 1576, 1549, 1492, 1456, 1427, 1399, 1367, 1319. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm, (*J*, Hz): 2.19 (3H, *s*, CH_3); 3.67 (2H, *s*, CH_2); 5.91 (1H, *s*, CH=); 7.02 (1H, *t*, *J* = 7.2, Ar H); 7.00 (1H, *t*, *J* = 7.3, Ph *p*-H); 7.08–7.24 (2H, *m*, Ph H); 7.49 (1H, *d*, *J* = 7.4, Ph H); 9.08 (1H, *s*, NH); 11.46 (1H, *s*, NH). ^{13}C NMR spectrum (100 MHz, DMSO-d_6, δ, ppm: 17.99 (CH_3); 32.00 (CH_2); 92.37 (C-2'); 124.36 (2C Ar); 125.78 (C Ar); 130.18 (C Ar); 130.77 (C Ar); 136.79 (C Ar), 153.92 (C-2); 165.40 (C=O), 174.18 (C=O). Found, %: C 58.05; H 4.87; N 11.28. $C_{12}H_{12}N_2O_2S$. Calculated, %: C 57.96; H 4.66; N 11.36.

(2Z)-*N*-benzyl-2-(3-methyl-4-oxo-1,3-thiazolidin-2-ylidene)acetamide (4a). Yield 0.50 g (64%), white powder, mp 183–186 °C. IR spectrum, ν, cm^{-1}: 3295 (NH), 1705 (C=O), 1635 (C=O), 1623, 1553, 1534, 1495, 1453, 1431, 1411, 1386, 1334. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm, (*J*, Hz): 3.04 (3H, *s*, CH_3); 3.72 (2H, *s*, CH2); 4.32 (2H, *d*, *J* = 5.4, CH_2N); 5.67 (1H, *s*, CH=); 7.22–7.34 (5H, *m*, Ph H); 8.22 (1H, *t*, *J* = 5.1, NH). ^{13}C NMR spectrum (100 MHz, DMSO-d_6, δ, ppm: 29.47 (CH_2); 31.10 (CH_3); 93.13 (C-2'); 126.70 (C Ar); 127.24 (C Ar); 128.25 (C Ar); 139.81 (C Ar); 153.08 (C-2), 166.19 (C=O), 172.12 (C=O). EI-MS *m*/*z* (%): 262 [M]$^+$ (90). Found, %: C 59.52; H 5.38; N 10.68. $C_{13}H_{14}N_2O_2S$. Calculated, %: C 59.32; H 5.37; N 10.56.

(2Z)-*N*-benzyl-2-(3-benzyl-4-oxo-1,3-thiazolidin-2-ylidene)acetamide (4b). Yield 0.31 g (76%), white powder, mp 144-147 °C. IR spectrum, ν, cm^{-1}: 3307 (NH), 1720 (C=O), 1649 (C=O), 1631, 1572, 1546, 1495, 1454, 1430, 1389, 1364, 1321. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm, (*J*, Hz): 3.86 (2H, *s*, CH_2); 4.25 (2H, *d*, *J* = 5.5, CH_2N); 4.79 (2H, *s*, CH_2N); 5.65 (1H, *s*, CH=); 7.21–7.37 (10H, *m*, Ph H); 8.17 (1H, *t*, *J* = 5.2, NH). ^{13}C NMR spectrum (100 MHz, DMSO-d_6, δ, ppm: 31.45 (CH_2); 42.49 (CH_2N); 46.38 (CH_2N); 94.32 (C-2'); 127.26 (C Ar); 127.90 (C Ar); 127.97 (C Ar); 128.75 (C Ar); 129.11 (C Ar); 135.56 (C Ar); 140.15 (C Ar); 152.47 (C-2), 166.53 (C=O), 173.21 (C=O). EI-MS *m*/*z* (%): 338 [M]$^+$ (23.79). Found, %: C 67.43; H 5.36; N 8.28. $C_{19}H_{18}N_2O_2S$. Calculated, %: C 67.38; H 5.35; N 8.41.

(2Z)-2-(3-methyl-4-oxo-1,3-thiazolidin-2-ylidene)-*N*-phenylacetamide (4c). Yield 0.22 g (79%), white powder, mp 209–211 °C (lit. 205–208 °C [26,27]). IR spectrum, ν, cm^{-1}: 3447 (NH), 1714 (C=O), 1650 (C=O), 1617, 1608, 1596, 1567, 1494, 1443, 1421, 1405, 1346, 13.11. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm, (*J*, Hz): 3.09 (3H, *s*, CH_3); 3.78 (2H, *s*, CH_2); 5.80 (1H, *s*, CH=); 7.00 (1H, *t*, *J* = 7.3, Ph p-H); 7.28 (2H, *t*, *J* = 7.7, Ph H); 7.60 (2H, *t*, *J* = 7.9, Ph H); 9.87 (1H, *s*, NH). ^{13}C NMR spectrum (100 MHz, DMSO-d_6), δ, ppm: 29.43 (CH_3); 31.00 (CH_3); 93.37 (C-2'); 118.50 (C Ar); 122.38 (C Ar); 128.45 (C Ar); 139.49 (C Ar); 154.76 (C-2), 164.79 (C=O), 171.95 (C=O). EI-MS *m*/*z* (%): 248 [M]$^+$ (31). Found, %: C 58.05; H 4.87; N 11.28. $C_{12}H_{12}N_2O_2S$. Calculated, %: C 58.27; H 5.07; N 11.45.

(2Z)-2-(3-benzyl-4-oxo-1,3-thiazolidin-2-ylidene)-*N*-phenylacetamide (4d). Yield 0.54 g (80%), white powder, mp 214–217 °C (lit. 216–218 °C [27]).

(2Z)-2-(3-benzyl-4-oxo-1,3-thiazolidin-2-ylidene)-*N*-(2-methylphenyl)acetamide (4e). Yield 0.37 g (76%), white powder, mp 166–169 °C. IR spectrum, ν, cm^{-1}: 3274.81, 3062.51, 1713.51 (C=O), 1653.91 (C=O), 1639.00, 1578.96, 1566.82, 1535.97, 1494.73, 1455.75, 1397.69, 1364.59, 1316.31. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm, (*J*, Hz): 2.16 (3H, *s*, CH_3); 3.90 (2H, *s*, CH_2); 4.85 (2H, *s*, CH_2N); 5.96 (1H, *s*, CH=); 7.02–7.48 (9H, *m*, Ar H); 9.06 (1H, *s*, NH). ^{13}C NMR spectrum (100 MHz, DMSO-d_6), δ, ppm: 17.93 (CH_3);

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31.02 (CH_2); 45.98 (CH_2N); 93.81 (C-2'); 124.08 (C Ar); 124.42 (C Ar); 125.84 (C Ar); 126.72 (C Ar); 127.51 (C Ar); 128.66 (C Ar); 130.22 (C Ar); 130.41 (C Ar); 135.04 (C Ar); 136.53 (C Ar); 153.86 (C-2); 165.00 (C=O); 172.78 (C=O). EI-MS *m/z* (%): 338 $[M]^+$ (8.83). Found, %: C 67.43; H 5.36; N 8.28. $C_{19}H_{18}N_2O_2S$. Calculated, %: C 67.58; H 5.20; N 8.19.

2.2. Study of fungicidal activity

The fungicidal activity of compounds **3a–c** and **4a–e** was tested *in vitro* on *Alternaria solani* Sorauer MFP601021, *Botrytis cinerea* Pers. MFG 60449, *Colletotrichum coccodes* JS 161-1, *Fusarium solani* (Mart.) Sacc. MFG 70523, *Phytophthora infestans* (Mont.) de Bary, *Plenodomus lingam* (Tode:Fr.) Höhn. MF Br17-044, *Rhizoctonia solani* RCAM01785 and *Sclerotinia sclerotiorum* using the agar block method. *P. infestans* was isolated at Nankai University (Tianjin, China). *C. coccodes* was purchased from the All-Russian Collection of Industrial Microorganisms (Moscow, Russia). The remaining strains of fungi were purchased from the Russian Collection of Agricultural Microorganisms (St. Petersburg, Russia).

Solutions of the tested compounds were prepared at a concentration of 0.5 mg/mL by dissolving 5 mg of the compound in 1 mL of DMSO with the addition of 9 mL of water. A total 1 mL of the test solutions was added to sterile Petri dishes containing 9 mL of heated (60 °C) nutrient medium and then mixed in a laminar flow cabinet. Fungal discs (4 mm in diameter) were cup under aseptic conditions from a 7-day-old culture of the test fungus using a sterile cork borer. The mycelium discs were placed in the center of Petri dishes containing the culture medium at room temperature. A negative control was prepared with the culture medium and DMSO. The fungi were incubated at 25 °C (48 h for *R. solani*, 120 h for *A. solani*, *P. lingam*, 72 h for other fungi). After incubation, the diameter of fungal colonies was measured. The percentage of fungus growth inhibition was determined by the formula [28]:

$$I\,(\%) = [(C - T)/(C - 4\ \text{mm})]\cdot 100, \qquad (1)$$

where I (%) – the degree of inhibition of mycelial growth, T (mm) – the mean value of the diameter of the colonies in the presence of a given concentration of each compound, and C (mm) – the mean diameter of the colonies in the absence of the compound under the same conditions. All the experiments were carried out in triplicate. The standard deviation was calculated.

The half maximal effective concentration for compound **4e** was determined by linear regression of the probability of the corresponding percentage of fungus radial growth from the logarithm of the concentration [29] in the GraphPad Prism 9.4.1 program. The commercial fungicide carbendazim, which is highly active against *P. lingam*, was used as a comparator agent.

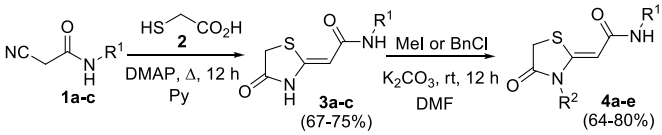
3. Results and Discussion

Compounds **3a–c** were obtained by reacting the corresponding cyanoacetamides **1a–c** with thioglycolic acid **2** in pyridine with the addition of dimethylaminopyridine as a catalyst according to a previously published procedure (Scheme 3 [25]. Further alkylation with methyl iodide or benzyl chloride in dimethylformamide in the presence of K_2CO_3 gave products **4a–e** in 64–80% yields.

The fungicidal activity of obtained compounds **3a–c** and **4a–e** was studied against 8 strains of phytopathogenic fungi that are widespread and cause significant damage to agriculture, such as *A. solani*, *B. cinerea*, *C. coccodes*, *F. solani*, *P. infestans*, *P. lingam*, *R. solani* and *S. sclerotiorum*.

An *in vitro* study of antifungal activity showed that most of the obtained compounds exhibit low ($I < 50\%$) or moderate ($50\% < I < 70\%$) activity against phytopathogenic fungi, inhibiting the growth of mycelium by 65% or less (Table 1).

However, compound **4e**, containing 2-methylphenyl at the nitrogen atom of the acetamide fragment and benzyl at the nitrogen atom of the thiazolidine ring, showed high activity against *A. solani* (causative agent of early blight of nightshade crops) and *P. lingam* (causative agent of cruciferous plants phomosis) with the inhibition degree of the fungi radial growth 75.77 and 85.94%, respectively.



1,3: R^1 = Bn (**a**); Ph (**b**); 2-MeC_6H_4 (**c**);
4: R^1 = Bn, R^2 = Me (**a**); R^1 = Bn, R^2 = Bn (**b**); R^1 = Ph, R^2 = Me (**c**); R^1 = Ph, R^2 = Bn (**d**); R^1 = 2-MeC_6H_4, R^2 = Bn (**e**)

Scheme 3 Synthesis of compounds **3a–c** and **4a–e**.

Table 1 Results of antifungal activity study *in vitro* for compounds **3a–c** and **4a–e** at a concentration of 50 μg/mL*.

Compounds	Degree of inhibition of mycelial growth (I±SD, %)							
	A. solani	*B. cinerea*	*C. coccodes*	*F. solani*	*R. solani*	*P. infestans*	*P. lingam*	*S. scleroti-*
3a	29.60±0.53	29.95±0.96	9.34±0.65	7.28±1.17	13.38±0.72	8.77±0.35	28.95±2.26	31.58±0.31
3b	37.80±0.60	32.50±1.21	4.20±0.77	9.63±0.99	9.75±0.68	5.48±0.60	1.95±0.16	6.06±0.94
3c	54.95±2.02	6.70±0.23	39.21±0.22	4.86±0.63	2.40±0.79	6.33±0.50	26.12±3.30	10.98±3.11
4a	37.22±2.63	12.25±0.67	58.65±0.18	1.08±1.12	9.76±0.77	10.25±0.21	43.45±2.48	17.01±1.04
4b	54.11±0.61	10.84±2.19	36.18±1.04	5.09±0.28	9.59±0.18	9.90±0.88	31.83±0.63	25.63±0.34
4c	51.73±1.56	8.21±0.76	47.04±0.52	3.42±0.38	0	12.33±1.12	30.59±1.15	64.45±2.10
4d	47.37±0.47	7.92±0.61	19.43±0.57	6.83±0.66	9.84±0.81	8.62±0.91	11.83±0.34	7.58±1.71
4e	75.77±0.39	22.89±1.00	54.47±0.11	8.74±0.96	3.27±0.32	10.23±1.38	85.94±0.06	34.09±0.91

*SD – standard deviation, I = 100 – active compound, I = 0 – in active compound.

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Half maximal effective concentration values of 1,3-thiazolidin-2-ylidene **4e** for *A. solani* and *P. lingam* were determined (Table 2).

Thus, promising results were obtained. Compound **4e** was found to have low EC_{50} values at the level of 1–2 μg/mL, comparable with commercial fungicides [30].

4. Limitations

In this paper, we present the first data on the antifungal activity of 2-(4-oxo-1,3-thiazolidin-2-ylidene)acetamide derivatives. The proposed approach for the preparation of potential fungicides is a one-step method for the synthesis of 2-(4-oxo-1,3-thiazolidin-2-ylidene)acetamide scaffold. This approachmakes it easy to modify the resulting compounds. Using this strategy makes it possible to obtain a wide range of compounds. Thus, this direction in the future will be followed so as to discover new compounds that are highly active against fungi. For targeted design of the potential fungicide structures based on the 2-(4-oxo-1,3-thiazolidin-2-ylidene)acetamides, additional studies of the mode of their biological action and identification of biological targets are required.

Also, it is necessary to perform further biological studies *in vivo* of the highly active compounds to evaluate their selectivity, toxicity to humans, animals and beneficial microorganisms, etc.

5. Conclusions

Thus, as a result of the work, we synthesized 8 derivatives of 2-(4-oxo-1,3-thiazolidin-2-ylidene)acetamide and studied their fungicidal activity *in vitro*. Compound **4e** was highly active against *A. solani* and *P. lingam*. It was shown that 2-(4-oxo-1,3-thiazolidin-2-ylidene)acetamides are promising base compounds for designing new fungicides.

• Supplementary materials

This article contains supplementary materials with copies of ^{1}H, and ^{13}C spectra, which are available on the corresponding online page.

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Table 2 Antifungal EC_{50} values of compound **4e**.

Fungi	Compounds	Regression equation	R^2	EC_{50}, μg/mL
A. solani	**4e**	$y = 1.4767x+9.5355$	0.9654	0.85
	CZ*	$y = 0.5110x+2.3270$	0.9794	>10000
P. lingam	**4e**	$y = 2.3053x+11.0900$	0.9881	2.29
	CZ	$y = 3.649x+15.7200$	0.9880	1.15

*CZ – commercial fungicide carbendazim.

• Author contributions

Conceptualization: K.L.O., T.V.G.
Data curation: K.L.O., T.A.K.
Formal Analysis: T.A.K.
Funding acquisition: T.A.K.
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Visualization: K.L.O.
Writing – original draft: K.L.O., T.A.K.
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• Conflict of interest

The authors declare no conflict of interest.

• Additional information

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