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Natural product-based fungicides discovery (II): Semisynthesis and biological activity of sarisan attached 3-phenylisoxazolines as antifungal agents

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Many phytopathogenic fungi cause severe damage to crop yields. In continuation of our research aimed at the discovery and development of natural products-based fungicides, a series of thirty-one sarisan attached 3-phenylisoxazolines were synthesized and evaluated for their antifungal activities against five phytopathogenic fungi (*B. cinerea*, *C. lagenarium*, *A. solani*, *F. solani*, and *F. graminearum*). Among all title sarisan derivatives, compounds **IV2**, **IV14** and **IV23** showed potent antifungal activity against some phytopathogenic fungi. In particular, compound **IV2** exhibited a broad-spectrum and more potent antifungal activity against *A. solani*, *F. solani,* and *F. graminearum* than the commercial fungicide Hymexazol. In addition, compounds **IV2**, **IV14** and **IV23** also displayed relative low toxicity on normal NRK-52E cells. This work will give some insights into the development of sarisan derivatives as new fungicide candidates in plant protection.

Keywords: Natural product • Sarisan derivative • Isoxazoline • Antifungal activity • Cytotoxic activity

Introduction

Many phytopathogenic fungi such as *Botrytis cinerea*, *Colletotrichum lagenarium*, *Alternaria solani*, *Fusarium solani*, and *Fusarium graminearum* infect crops, are hard to control and results in severe damages to crop yields.[1-4] Although many synthetic chemical fungicides play an important role in plant diseases control, repeated use of these agents has led to the increase of drug-resistance and other detrimental effects on the environment and human beings.[5,6] Thus, there is an urgent need for the discovery of effective, low mammalian toxicity, and ecofriendly fungicide alternatives to address the plant diseases problems.

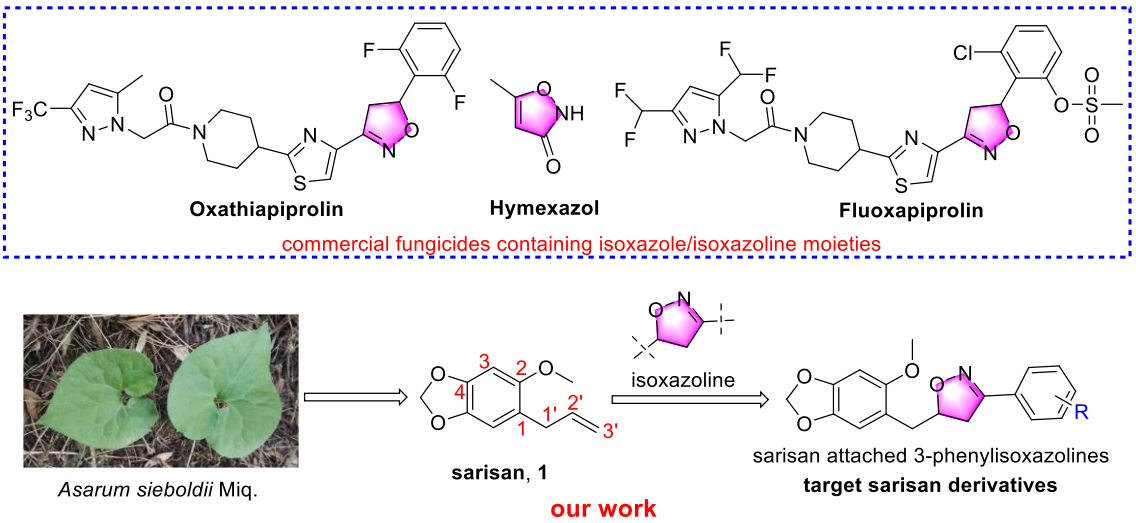


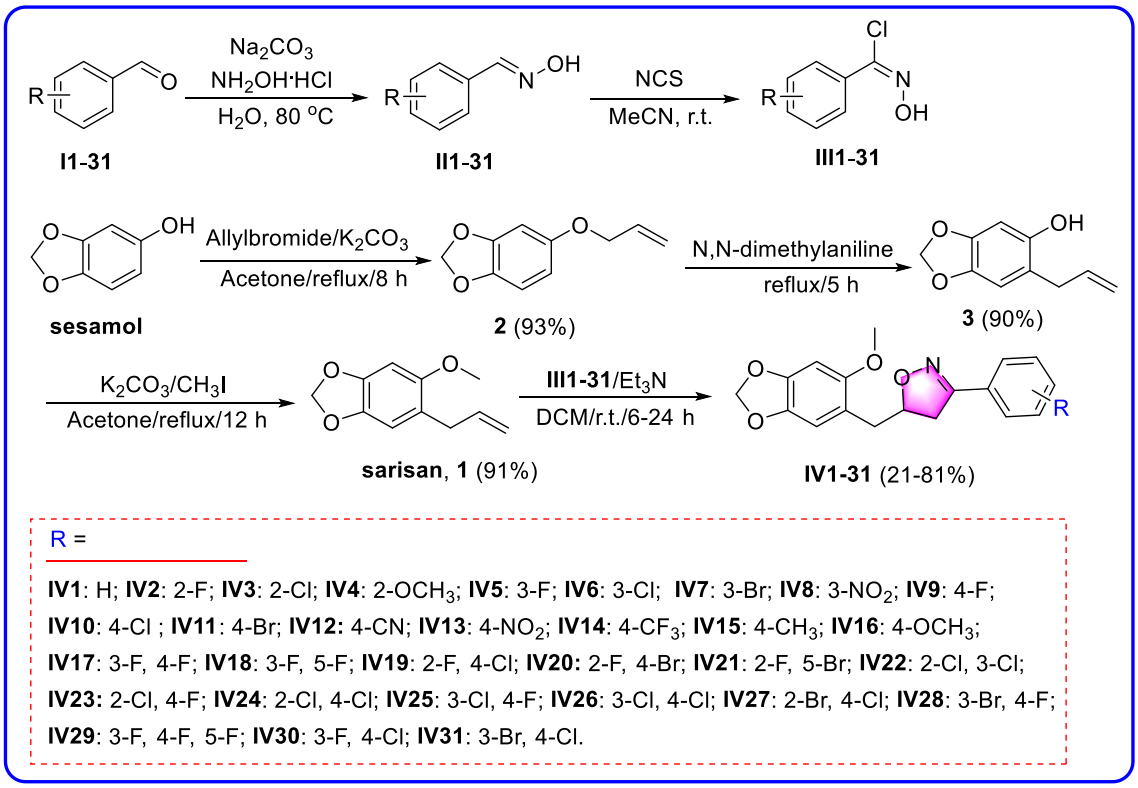
Figure 1. Design of the sarisan attached 3-phenylisoxazolines.

Natural products (NPs) have a long history of being used as sources for the development of pesticides due to their low toxicities to non-target organism and ecofriendly properties.[7,8] Therefore, using natural products or their derivatives to develop new fungicides has been becoming a hot topic in recent years. Sarisan (**1**, **Figure 1**), a naturally occurring lignan compound, is isolated from many plants such as *Asarum sieboldii*,[9] *Piperguineense*,[10] *Piper solmsianum* C.DC,[11] *Beilschmiedia miersii*,[12] and *Saururus chinensis*.[13] Compound **1** has been reported to possess many biological activities including

antimicrobial activity, psychopharmacologic effect, and anti-septic activity, but the most noteworthy is its insecticidal and antifungal activities.[14-18] In addition, isoxazole and isoxazoline are important active *N*-heterocycles for the development of novel pesticides. Oxathiapiprolin and Fluoxapiprolin (Figure. 1), discovered by Bayer AG and DowDuPont Inc., respectively, are two new isoxazoline fungicides.[19,20] Hymexzaol (**Figure. 1**) is commercially known as Tachigaren, and it is a widely used fungicide to control many plant diseases. Based on the above mentioned, and in our continuous efforts to develop natural product-based pesticides,[21-24] herein, we have prepared a series of novel sarisan attached 3-phenylisoxazolines and evaluated for their antifungal and cytotoxic activities.

Results and Discussion

Chemistry



Scheme 1. Synthetic route of sarisan attached 3-phenylisoxazolines **IV1–31**.

As shown in **Scheme 1,** the key intermediates *N*-hydroxybenzimidoyl chlorides **III1–31** were prepared through two steps according to the previously reported procedures.[25] First, different substituted benzaldehydes **I1–31** reacted with hydroxylamine hydrochloride ($NH_2OH·HCl$), respectively, in the presence of Na_2CO_3 in EtOH at reflux to acquire the corresponding benzaldoximes **II1–31**. Then, chlorination of benzaldoximes **II1–31** *N*-chlorosuccinimide (NCS) to give the key intermediates **III1–31**. The sarisan was synthesized by using sesamol as the starting material through etherification, Claisen rearrangement and methylation as our previous report.[26] Finally, [3+2] cyclization of sarisan (**1**) and the corresponding *N*-hydroxybenzimidoyl chlorides **III1–31** with Et_3N in anhydrous dichloromethane under N_2 to obtain the target derivatives **IV1–31** in 21–81% yields. All target derivatives **IV1–31** were determined by melting point (m.p.) IR, $^1H/^{13}C$ NMR, and ESI-MS spectral analyses. Moreover, the stereo structure of **IV23** (CCDC 2026211) was unambiguously identified by X-ray diffraction (**Figure 2**).

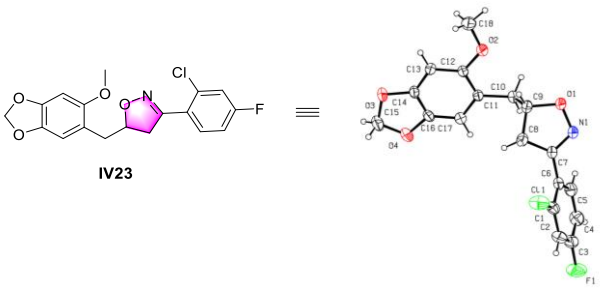


Figure 2. X-ray crystal structure of compound **IV23**.

Antifungal and Cytotoxic Activities

The antifungal activity of the title compounds **IVI–31** against five phytopathogenic fungi (*B. cinerea*, *C. lagenarium*, *A. solani*, *F. solani*, and *F. graminearum*) was preliminarily evaluated at a concentration of 50 μg/mL using the mycelium growth rate method with a commercial fungicide Hymexazol as the positive control.[21] In general, as the **Table 1** displays, we found that most sarisan attached 3-phenylisoxazolines showed more potent antifungal activity against *B. cinerea* and *C. lagenarium* than the precursor sarisan after structural modification. For example, all title sarisan derivatives except compounds **IV9**, **IV12**, **IV20**, **IV22** and **IV25** displayed more potent antifungal activity against *B. cinerea* than sarisan (inhibition rate: 28.5%); towards derivatives **IVI–31** against *C. lagenarium*, twenty-one target derivatives exhibited more potent antifungal activity against *C. lagenarium* than sarisan (inhibition rate: 34.4%). Among all title derivatives **IVI–31**, compounds **IV7**, **IV23** and **IV30** exhibited potent antifungal activity against *B. cinerea* with the inhibition rates of 67.4%, 67.9% and 61.4%, respectively, which is better than the commercial fungicide Hymexazol (inhibition rate: 55.3%). Compounds **IV4**, **IV10**, **IV13**, **IV22**, **IV23**, **IV25**, **IV26** and **IV29** displayed more potent antifungal activity against *C. lagenarium* than the positive control Hymexazol, their inhibition rates were 43.0%, 44.4%, 43.7%, 43.5%, 59.6%, 43.5%, 49.4% and 59.6%, respectively. To our delight, we found that compound **IV2** exhibited more potent and broad-spectrum antifungal activity against three phytopathogenic fungi (*A. solani*, *F. solani,* and *F. graminearum*) with the inhibition rates all greater than 50%. In addition, compound **IV14** showed more promising antifungal activity against both *A. solani* and *F. graminearum* with inhibition rates of 55.7%, and 53.1%, respectively. Compound **IV16** exhibited potent antifungal activity against *F. graminearum* with the inhibition rate of 53.1%.

Table 1. Antifungal activity of **IV1–31** against five phytopathogenic fungi at 50 μg/mL[a]

Compound	Inhibition rate (% ± SD)				
	B. cinerea	*C. lagenarium*	*A. solani*	*F. solani*	*F. graminearum*
IV1	41.9 ± 4.4	41.4 ± 0.04	53.1 ± 1.5	24.1 ± 1.3	40.7 ± 1.9
IV2	45.5 ± 2.1	39.2 ± 0.03	54.3 ± 4.0	55.0 ± 3.5	55.9 ± 1.1
IV3	41.6 ± 1.7	35.0 ± 3.0	41.4 ± 6.0	22.5 ± 7.1	43.0 ± 1.1
IV4	35.3 ± 1.4	43.0 ± 5.4	54.3 ± 2.1	15.0 ± 3.5	23.3 ± 4.7
IV5	43.2 ± 2.2	33.7 ± 1.4	33.8 ± 2.1	35.0 ± 3.5	33.1 ± 1.1
IV6	32.1 ± 5.1	31.5 ± 1.6	20.6 ± 4.5	19.3 ± 1.6	38.6 ± 2.4
IV7	67.4 ± 3.6	36.1 ± 1.3	9.3 ± 0.04	22.2 ± 1.6	35.3 ± 4.1
IV8	36.2 ± 2.3	32.2 ± 1.6	13.2 ± 2.1	24.7 ± 2.2	23.7 ± 2.0
IV9	19.0 ± 0.6	30.1 ± 2.3	32.7 ± 3.1	22.3 ± 1.3	23.9 ± 1.7
IV10	31.6 ± 3.8	44.4 ± 1.3	31.0 ± 2.7	18.3 ± 4.7	29.5 ± 1.4
IV11	42.4 ± 2.4	17.7 ± 1.8	30.0 ± 2.0	20.0 ± 3.7	22.1 ± 4.0
IV12	20.3 ± 3.8	39.8 ± 1.3	33.6 ± 2.7	28.3 ± 1.3	30.0 ± 3.5
IV13	42.0 ± 1.8	43.7 ± 1.6	20.6 ± 4.6	40.6 ± 4.6	23.1 ± 2.2
IV14	43.7 ± 1.9	27.6 ± 2.2	55.7 ± 2.0	25.0 ± 3.5	50.8 ± 1.1
IV15	37.4 ± 2.0	36.7 ± 3.6	16.2 ± 2.0	37.8 ± 2.2	44.6 ± 3.2
IV16	40.3 ± 1.3	38.0 ± 1.8	45.7 ± 0.03	15.0 ± 0.02	53.1 ± 2.2
IV17	47.5 ± 0.03	34.5 ± 1.6	17.6 ± 4.2	44.1 ± 2.2	33.4 ± 0.5
IV18	45.9 ± 1.8	39.8 ± 1.4	27.9 ± 2.1	42.5 ± 3.5	46.0 ± 2.1
IV19	44.5 ± 2.4	37.8 ± 1.4	14.7 ± 0.04	43.8 ± 1.8	46.8 ±1.8
IV20	21.1 ± 3.1	38.0 ± 1.3	14.7 ± 3.8	41.5 ± 1.6	38.5 ± 0.03
IV21	35.9 ± 1.6	28.7 ± 1.3	13.3 ± 1.9	22.2 ± 1.2	27.9 ± 1.5
IV22	20.5 ± 3.6	43.5 ± 3.9	22.7 ± 0.04	29.0 ± 1.4	32.9 ± 1.8
IV23	67.9 ± 5.1	59.6 ± 0.04	17.5 ± 4.5	42.2 ± 1.6	45.5 ± 2.6
IV24	43.1 ± 2.2	32.2 ± 1.6	14.7 ± 0.02	26.2 ± 0.04	16.8 ± 3.4
IV25	25.0 ± 0.9	43.5 ± 3.9	17.3 ± 0.03	43.0 ± 1.6	37.3 ± 1.5
IV26	35.7 ± 0.03	49.4 ± 1.6	12.7 ± 2.2	13.6 ± 3.2	28.3 ± 2.8
IV27	38.3 ± 0.02	39.2 ± 0.02	19.0 ± 2.4	22.3 ± 1.6	16.5 ± 3.2
IV28	46.4 ± 2.1	31.5 ± 1.6	14.3 ± 0.04	39.3 ± 2.2	37.2 ± 2.9
IV29	32.1 ± 1.8	59.6 ± 0.03	0 ± 0	43.1 ± 1.6	34.0 ± 3.1
IV30	61.4 ± 2.1	40.8 ± 0.04	25.0 ± 2.1	45.0 ± 3.5	47.7 ± 0.02
IV31	37.4 ± 1.3	33.7 ± 1.4	17.6 ± 4.2	40.3 ± 1.8	40.0 ± 1.1
Sarisan	28.5 ± 2.2	34.4 ± 2.9	35.2 ± 1.3	38.5 ± 3.1	45.3 ± 2.5
Hym[b]	55.3 ± 2.4	42.1 ± 1.4	38.3 ± 1.5	46.4 ± 2.0	54.5 ± 1.1

[a] Values are means ± SD of three replicates; [b] Hymexazol was used as a positive control.

Moreover, in order to investigate the antifungal activity of some potent sarisan attached 3-phenylisoxazolines more accurately, EC_{50} values of compounds **IV2**, **IV14** and **IV23** against five phytopathogenic fungi were further screened. As shown in **Table 2**, compound **IV2** exhibited more potent antifungal activity

against three phytopathogenic fungi (*A. solani*, *F. solani*, and *F. graminearum*) with the EC_{50} values of 32.9 ± 1.6, 35.6 ± 0.3, and 33.4 ± 0.4 μg/mL, respectively, than the commercial fungicide Hymexazol. Compound **IV14** showed better antifungal activity against *A. solani* with EC_{50} value of 37.0 ± 1.0 μg/mL than the Hymexazol (EC_{50}: 69.9 ± 2.0 μg/mL). The EC_{50} values of compound **IV23** against *B. cinerea* and *C. lagenarium* were 30.1 ± 0.7 and 36.6 ± 0.9 μg/mL, respectively, whereas, the EC_{50} values of Hymexazol against *B. cinerea* and *C. lagenarium* were 41.2 ± 0.5 and 65.7 ± 1.6 μg/mL, respectively. This result indicated **IV23** had better antifungal activity against *B. cinerea* and *C. lagenarium* than Hymexazol. In addition, effects of compound **IV2** on the growth of *A. solani*, *F. solani* and *F. graminearum* at different concentrations were displayed in **Figure 3**. It is apparent that the inhibition effects of compound **IV2** against *A. solani*, *F. solani* and *F. graminearum* increased in a concentration dependent manner. Given the potent activity of compound **IV2**, it could be used as a potential antifungal agent to protect some crops that are susceptible to fungi *A. solani*, *F. solani* and *F. graminearum*, such as tomatoes, potatoes and wheat.

Table 2. The EC50 values of **IV2**, **IV14**, **IV23** and Hymexazol against five phytopathogenic fungi.

Compound	EC_{50} ± SD (μg/mL) [a]				
	B. cinerea	*C. lagenarium*	*A. solani*	*F. solani*	*F. graminearum*
IV2	/ [b]	/	32.9 ± 1.6	35.6 ± 0.3	33.4 ± 0.4
IV14	/	/	37.0 ± 1.0	/	36.8 ± 0.5
IV23	30.1 ± 0.7	36.6 ± 0.9	/	/	/
Hym [c]	41.2 ± 0.5	65.7 ± 1.6	69.9 ± 2.0	49.6 ± 1.9	34.6 ± 1.2

[a] 50% Effective concentration: concentration of compound that inhibits the fungi growth by 50%; [b] /: not detected; [c] Hymexazol was used as a positive control.

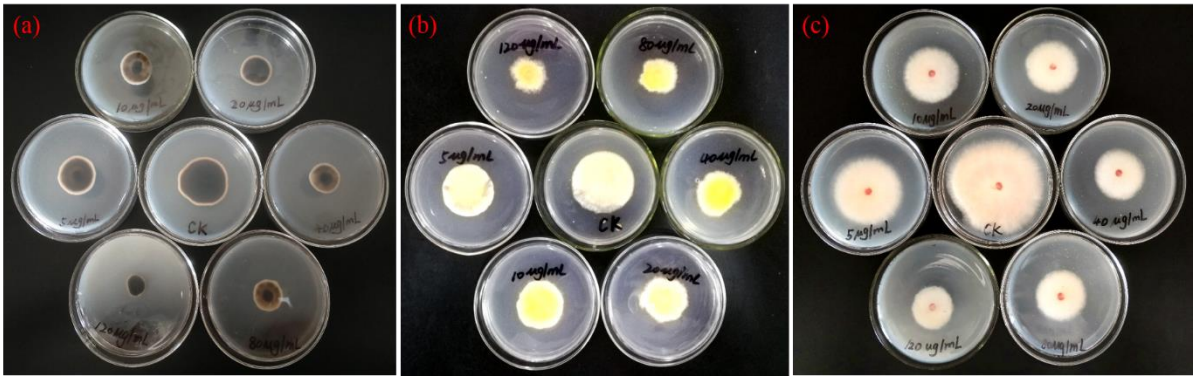


Figure 3. The inhibition effect of compound **IV2** at different concentrations against *A. solani* (a), *F. solani* (b) and *F. graminearum* (c), CK: blank control group.

To explore the detrimental effects of these sarisan attached 3-phenylisoxazolines on normal mammalian cells, three potent compounds **IV2**, **IV14** and **IV23** were further investigated for their cytotoxicities on normal NRK-52E cells using CCK-8 method.[27] As displayed in **Figure. 4**, when NRK-52E cells were treated with different concentrations of compounds **IV2**, **IV14** and **IV23**, the NRK-52E cells still remained high viabilities. These resluts indicated that these sarisan attached 3-phenylisoxazolines showed relative low toxicity on normal NRK-52E cells, and had selectivity between phytopathogenic fungi and normal mammalian cells.

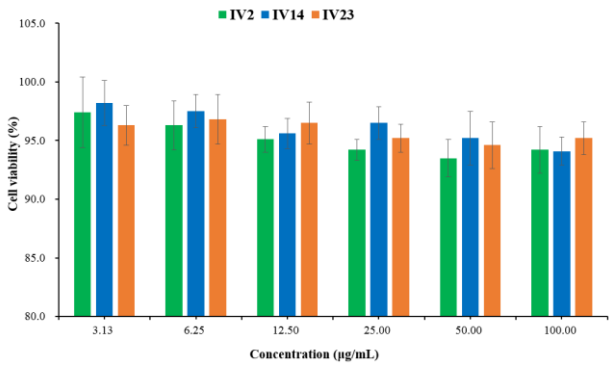


Figure 4. Relative cell viabilities of NRK-52 cells treated with compounds **IV2**, **IV14** and **IV23**.

Conclusions

In summary, we have synthesized a series of thirty-one sarisan attached 3-phenylisoxazolines **IV1**–**31**, and determined their structures by different spectral analyses of $^{1}H/^{13}C$ NMR, IR and ESI-MS. All title sarisan attached 3-phenylisoxazolines **IV1**–**31** were evaluated for their antifungal activities against five phytopathogenic fungi (*B. cinerea*, *C. lagenarium*, *A. solani*, *F. solani*, and *F. graminearum*). Among all title sarisan derivatives, compounds **IV2**, **IV14** and **IV23** showed more promising antifungal activity against some phytopathogenic fungi than the commercial fungicide Hymexazol. In particular, compound **IV2** exhibited a broad-spectrum and potent antifungal activity against three phytopathogenic fungi (*A. solani*, *F. solani,* and *F. graminearum*) with the EC_{50} values of 32.9 ± 1.6, 35.6 ± 0.3, and 33.4 ± 0.4 μg/mL, respectively. In addition, compounds **IV2**, **IV14** and **IV23** also displayed relative low toxicity on normal NRK-52E cells. These resluts indicated that the potent sarisan attached 3-phenylisoxazolines **IV2**, **IV14** and **IV23** had selectivity between phytopathogenic fungi and normal mammalian cells. This work will pave the way for the development of sarisan derivatives as fungicide candidates in plant protection.

Experimental Section

Instruments and Reagents

^{1}H NMR/^{13}C NMR spectra of all sarisan derivatives **IV1**–**31** were recorded on a Bruker 400/100 MHz instrument (Avance 400 MHz, Bremerhaven, Germany). Infrared (IR) spectra were detected by a PE-1710 FT-IR spectrometer. A Microplate Reader (Tecan Infinite Pro series M200) was used to record optical density and fluorescence. Sesamol was purchased from Aladdin Bio-Chem Technology Co., Ltd. (Shanghai, China). Anhydrous solvents were dried and purified according to standard methods before use. Other chemicals were of analytical grade and all obtained from commercial resources.

Synthesis of Sarisan Attached 3-Phenylisoxazolines **IV1**–**31**

Sarisan and the intermediates *N*-hydroxybenzimidoyl chlorides **III1**–**31** were prepared as our previously reported procedures.[24, 25] Then, to a solution of sarisan (0.5 mmol, 96.1 mg) in CH_2Cl_2 (10 mL) under N_2, the corresponding *N*-hydroxybenzimidoyl chlorides **III1**–**31** (0.55 mmol) and trimethylamine (0.55 mmol, 55.7 mg) were added. The mixture was stirred for 6–24 h at room temperature (r.t.). When the reaction was complete, the solvent was concentrated and then purified by PTLC with developing solvents petroleum ether: ethyl acetate = 3: 1 (v/v) to give the target derivatives **IV1**–**31** in 21–81% yields. Examples of spectra data of **IV1**–**3** are shown below, whereas data of other derivatives **IV4**–**31** are listed in *Supporting Information*.

Data for **IV1**: Gray solid, yield: 81%, m.p. 90-92°C; IR cm^{-1} (KBr): 2916, 1621, 1487, 1354, 1290, 1196, 1031, 923, 845, 757, 690; ^{1}H NMR (400 MHz $CDCl_3$) δ: 7.65-7.62 (m, 2H, -Ar), 7.39-7.38 (m, 3H, -Ar), 6.72 (s, 1H, -Ar), 6.52 (s, 1H, -Ar), 5.90 (s, 2H, -OC*H*$_2$O-), 5.01-4.94 (m, 1H, H-5′), 3.76 (s, 3H, -OC*H*$_3$), 3.30-3.23 (m, 1H, H-4′), 3.09-3.05 (m, 1H, H-6′), 3.03-3.00 (m, 1H, H-4′), 2.85-2.80 (m, 1H, H-6′); ^{13}C NMR (100 MHz $CDCl_3$) δ: 156.5, 152.5, 146.9, 140.9, 129.9, 128.6, 126.6, 110.9, 101.0, 94.6, 80.9, 56.2, 39.2, 35.2, 35.3; MS (ESI) m/z calcd for $C_{18}H_{18}NO_4$ ($[M+H]^+$) 312.1, found 312.1.

Data for **IV2**: Yellow solid, yield: 38%, m.p. 52-54°C; IR cm^{-1} (KBr): 2924, 1596, 1488, 1456, 1195, 1036, 931, 761; ^{1}H NMR (400 MHz $CDCl_3$) δ: 7.84-7.80 (m, 1H, -Ar), 7.39-7.33 (m, 1H, -Ar), 7.17-7.13 (m, 1H, -Ar), 7.11-7.06 (m, 1H, -Ar), 6.72 (s, 1H, -Ar), 6.51 (s, 1H, -Ar), 5.89 (s, 2H, -OC*H*$_2$O-), 5.00-4.93 (m, 1H, H-5′), 3.76 (s, 3H, -OC*H*$_3$), 3.39-3.32 (m, 1H, H-4′), 3.19-3.13 (m, 1H, H-6′), 3.02-2.97 (m, 1H, H-4′), 2.86-2.81 (m, 1H, H-6′); ^{13}C NMR (100 MHz CDCl3) δ: 161.5, 159.0, 153.3, 152.5, 146.9, 140.9, 131.4, 129.0, 124.3, 117.9, 117.2, 116.4, 116.2, 110.9, 101.0, 94.5, 81.1, 56.2, 41.0, 35.2; MS (ESI) m/z calcd for $C_{18}H_{17}FNO_4$ ($[M+H]^+$) 330.1, found 330.3.

Data for **IV3**: Gray solid, yield: 24%, m.p. 121-123°C; IR cm^{-1} (KBr): 2936, 1622, 1498, 1486, 1196, 1035, 927, 852, 763; ^{1}H NMR (400 MHz $CDCl_3$) δ: 7.59-7.56 (m, 1H, -Ar), 7.41-7.39 (m, 1H, -Ar), 7.34-7.27 (m, 2H, -Ar), 6.74 (s, 1H, -Ar), 6.51 (s, 1H, -Ar), 5.90 (s, 2H, -OC*H*$_2$O-), 5.04-4.96 (m, 1H, H-5′), 3.76 (s, 3H, -OC*H*$_3$), 3.45-3.38 (m, 1H, H-4′), 3.25-3.19 (m, 1H, H-6′), 3.05-3.00 (m, 1H, H-4′), 2.88-2.83 (m, 1H, H-6′); ^{13}C NMR (100 MHz CDCl3) δ: 156.5, 152.2, 146.9, 140.9, 132.8, 130.4, 129.5, 126.9, 117.1, 111.0, 101.0, 94.5, 81.5, 56.2, 41.7, 35.0; MS (ESI) m/z calcd for $C_{18}H_{17}{}^{35}ClNO_4$ ($[M+H]^+$) 346.0, found 346.1, $C_{18}H_{17}{}^{37}ClNO_4$ ($[M+H]^+$) 348.0, found 348.1.

Antifungal and Cytotoxic Activities

The antifungal activity of all title sarisan attached 3-phenylisoxazolines **IV1**–**31** against five phytopathogenic fungi was evaluated by using the mycelium growth rate method according to our previous report.[21] PDA medium was prepared through using potato dextrose agar and then sterilized at 115 °C for 30 min. Each fungus was incubated in PDA at 28 ± 1 °C for about 5 days to get new mycelium for the antifungal assays, and then using a sterilized puncher to cut a mycelia disk of approximately 5 mm diameter from culture medium. Subsequently, the mycelia disk was inoculated in the center of the PDA Petri dishes. The tested derivatives **IV1**–**31** and Hymexazol were dissolved in acetone, then mixed with the medium to set at the final concentration of 50 μg/mL. The mixed medium was then added to the sterilized Petri dishes. The inoculated Petri dishes were incubated at 28±1 °C for 3 days. Acetone with only PDA was served as a blank control (CK); the commercial fungicide Hymexazol was used as the positive control. Each treatment was conducted with three

replicates. Finally, The radial growths of the fungal colonies were measured by a vernier caliper. The cytotoxic activity of compounds **IV2**, **IV14** and **IV23** against NRK-52E cells was assessed by the reported CCK-8 (Sigma-Aldrich,Germany) method.[27] In brief, 5×10^3 NRK-52E cells (Shanghai Cell Bank, Chinese Academy of Sciences) in 100 μL medium were added to a 96-well plates. Subsequently, these cells were incubation at 37 °C for 24 h, a 100 μL of fresh medium with the compounds **IV2**, **IV14** and **IV23** in different concentration was added to remove and replace the used culture medium. The negative control was only added fresh medium. After incubation for 24 h, the used culture medium was discarded, and then using the new culture medium to wash the used medium twice. Finally, new medium containing 5% CCK-8 (100 μL) was added to each well. The cells were cultured at 37 °C for a further 4 h and then the absorbance at 450 nm was measured using a Microplate Reader.

Data and statistical analysis

The Inhibition rates of compounds IV1–31 against five phytopathogenic fungi were calculated by the following formula: Inhibition rate (%) = (C–T) × 100/(C–5 mm), where C is the diameter of fungi growth on untreated PDA, and T represents the diameter of fungi on treated PDA. The relative cell viability was calculated with the formula: Cell viability rate (%) = $(OD_{experiment} - OD_{blank})/(OD_{negative\ control} - OD_{blank}) \times 100\%$. All data are expressed as mean ± SD, and each group was performed three times. Statistical analysis was processed by the SPSS 21.0 software (SPSS Inc., Chicago, USA).

Supplementary Material

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/MS-number.

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Author Contribution Statement

Zhiyan Liu and Xiaoguang Wang prepared the sarisan derivatives. Jiangping Cao provided some phytopathogenic fungi samples and performed part of antifungal activity assays. Zhiyan Liu, Xiaoting Yan, and Wanqing Cheng also performed part of antifungal and cytotoxic activities assays, and then analyzed the data. Ruige Yang and Yong Guo conceived the experiments, and wrote the manuscript. All authors approved the final version of the manuscript.

Declaration of competing interest

The authors declare no competing financial interest.

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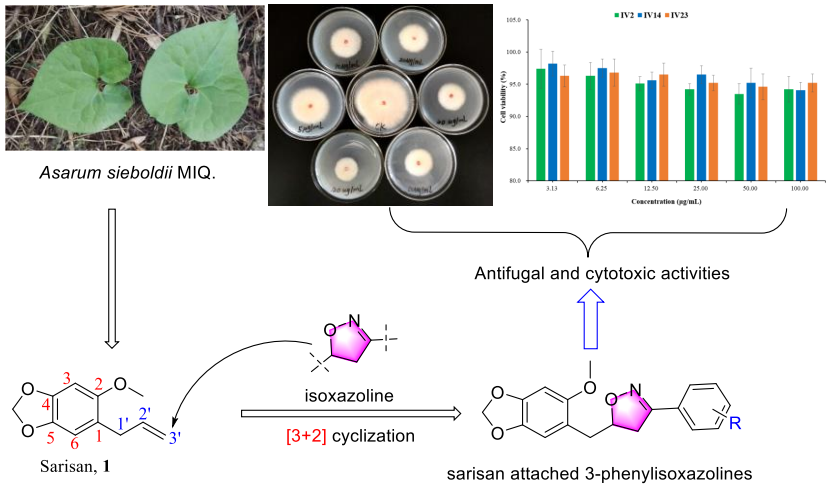

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A series of sarisan attached 3-phenylisoxazolines with potent antifungal activity against against some phytopathogenic fungi.