Synthesis and Antifungal Activities of Biquinazoline Diselenides Compounds

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Síntesis y actividades antifúngicas de los compuestos de diselenuros de biquinazolina

Síntesi i activitats antifúngiques dels compostos de diselenurs de biquinazolina

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SUMMARY

A series of novel biquinazoline diselenide compounds was designed and synthesized with substituted 4-chloroquinazoline and sodium diselenide. Their structures were confirmed by IR, ^{1}H NMR, ^{13}C NMR, and elemental analyses. The antifungal activity of the new compounds was evaluated by growth-rate method *in vitro*. Compound **1b, 1c, 1d, 1h**, **1i** and **1j** were found to have activities against nine kinds of phytopathogenic fungi cell lines, *G. zeae, F. oxysporum, C. mandshurica, R. solani, T. cucumeris, S. sclerotiorum, B. cinerea, P. infestans* and *C. gloeosporioides*. Moreover, compared with the commercial antifungal drugs Hymexazol, **1b** exerted better antifungal effects on corresponding bacterial lines at 50 μg/mL.

Keywords: Quinazoline; biquinazoline diselenide; synthesis; antifungal activities.

RESUMEN

Una serie de compuestos nuevos de diselenuros de biquinazolina ha sido diseñada y sintetizada con sustitutos como la 4-cloroquinazolina y el diselenuro de sodio. Sus estructuras se confirmaban mediante IR, ^{1}H NMR, ^{13}C NMR, y análisis elementales. La actividad antifúngicas de los nuevos compuestos se evaluaba mediante el método del ritmo de crecimiento *in vitro*. Los compuestos **1b, 1c, 1d, 1h, 1i** y **1j** presentaban actividades frente a nueve tipos de lineas celulares de hongos fitopatógenos, *G. zeae, F. oxysporum, C. mandshurica, R. solani, T. cucumeris, S. sclerotiorum, B. cinerea, P. infestans* y *C. gloeosporioides.* Además, en comparación con los fármacos antifúngicos comerciales, el Hymexazol, **1b** tenía unos efectos antifúngicos mejores en las correspondientes líneas bacterianas a 50 μg/mL.

Palabras clave: Quinazolina; diselenuro de biquinazolina; síntesis; actividades antifúngicas.

RESUM

Una sèrie de compostos nous de diselenurs de biquinazolina ha sigut dissenyada i sintetitzada amb substituts com la 4-cloroquinazolina i el diselenur de sodi. Les seves estructures es confirmaven mitjançant IR, ^{1}H NMR, ^{13}C NMR, i anàlisis elementals. Les activitats antifúngiques dels nous compostos era avaluada mitjançant el mètode del ritme de creixement *in vitro*. Els compostos **1b, 1c, 1d, 1h, 1i** y **1j** presentaven activitats davant nou tipus de línies cellulars de fongs fitopatògens, *G. zeae, F. oxysporum, C. mandshurica, R. solani, T. cucumeris, S. sclerotiorum, B. cinerea, P. infestans* i *C. gloeosporioides.* A més, en comparació amb els fàrmacs antifúngics comercials, el Hymexazol, **1b** tenia millor efectes antifúngics en les corresponents línies bacterianes a 50 μg/mL.

Paraules clau: Quinazolina; diselenur de biquinazolina; síntesi; activitats antifúngiques.

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INTRODUCTION

Quinazoline compounds are a series of small-molecule drugs with good biological activities in medicals [1-3] and pesticides [4,5] in recent years. As part of our ongoing research on heterocyclic compounds, we were particularly interested in 4-substituted quinazolines from O, N, S and Se atom [6-8]. Their activities are found to vary, but bioactivities of anticancer and antifungal is not significantly reduced. Selenide compounds especially heterocyclic containing-selenium compounds exert multi-targeted anticancer effects through various mechanisms [9,10]. Some selenide drugs that are currently undergoing clinical studies include Ebselen [11], which has anti-inflammatory and antioxidant properties, and Selenazofurin [12], which has antiviral and antitumor properties. New selenium-containing drugs emerged gradually in recent years [13-16].

According to bio-electronic line principle, we had designed and synthesized a series of novel biquinazoline diselenide compounds considering the multi-mechanism and multi-targeting anticancer effects of organoselenium compounds, together with the good inhibitory activity of EGFR quinazoline compounds [17-19]. In this paper, a series of biquinazoline diselenide compounds was prepared with substituted 4-chloroquinazoline and sodium diselenide (**Scheme 1**). The structures of the new compounds were confirmed by elemental analysis, IR, ^{1}H NMR, and ^{13}C NMR. The antifungal activities of the new compounds were evaluated by growth-rate method *in vitro*. Among them, compound **1b, 1c, 1d, 1h, 1i** and **1j** showed good activities against *Gibberella zeae*, *Fusarium oxysporum*, *Cytospora mandshurica*, *Rhizoctonia solani*, *Thanatephorus cucumeris, Sclerotina sclerotiorum, Botrytis cinerea, Phytophthora infestans* and *Colletotrichum gloeosporioides*. The inhibition activity of **1b** against all of the bacterial cell lines was more than 50% at 50 μg/mL concentration, better than or comparable with the commercial antifungal drugs Hymexazol.

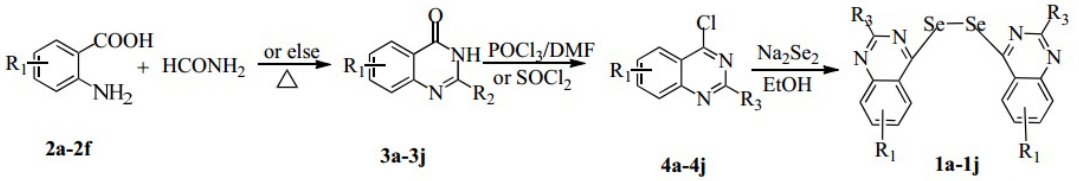
RESULTS AND DISCUSSION

The synthesis of intermediates **3a, 3b, 3c, 3d, 3h** and **3i** from anthranilic acid or substituted anthranilic acid reacted with formamide. The synthesis of intermediates **3e** and **3j** from anthranilic acid (**2a**) or substituted anthranilic acid reacted with urea. The synthesis of intermediate **3f** from anthranilic acid reacted with acetic anhydride, and then reacted with ammonium acetate. The synthesis of intermediates **3g** needs three steps from **2a.** Firstly anthranilic acid reacted with benzoyl chloride, and then reacted with aqua ammonia, finally reacted with sodium hydroxide. In chlorination step, synthesis of **4e**, **4g** and **4j** must needed phosphorus oxychloride catalyzing by dimethylformamide. The others intermediates needed thionyl chloride catalyzing by dimethylformamide.

Unfortunately, the yields of the synthesis of diselenide compounds were not ideal below in 50%. Some products were insoluble in ethanol during the reaction. It's as a by-product after the analysis, most probably were quinazoline diselenide sodium compounds. Based on literature [20], the yields of synthesis of bibenzyl diselenides by using benzyl chloride or benzyl bromide as starting materials were very good. But using 4-chloroquinazoline compounds as starting materials, the yields of synthesis of biquinazoline diselenide compounds were not achieve the desired goals. The yields remained low changing the reaction conditions, which itself quinazoline ring large size had an important effect. The novel biquinazoline diselenide compounds were the symmetrical structure of compounds. Based on analysis of ^{1}H NMR and ^{13}C NMR spectrogram, H and C chemical shift had the same position in both quinazoline groups.

G. zeae, F. oxysporum, C. mandshurica, R. solani, T. cucumeris, S. sclerotiorum, B. cinerea, P. infestans and *C. gloeosporioides* were used for antifungal drug discovery screening through growth-rate method *in vitro*. **Table 1** showed that **1b, 1c, 1d, 1h, 1i** and

Scheme 1 *Synthesis of biquinazolin-4-yl diselenide compounds*



2a-2f

2a: R_1=H;
2b: R_1=5-Cl;
2c: R_1=5-Br;
2d: R_1=5-I;
2e: R_1=3,5-Cl_2;
2f: R_1=3,5-Br_2 .

3a-3j

3a: R_1=H, R_2=H;
3b: R_1=6-Cl, R_2=H;
3c: R_1=6-Br, R_2=H;
3d: R_1=6-I, R_2=H;
3e: R_1=H, R_2=OH;
3f: R_1=H, R_2=CH_3;
3g: R_1=H, R_2=Ph;
3h: R_1=6,8-Cl_2, R_2=H;
3i: R_1=6,8-Br_2, R_2=H;
3j: R_1=6-Cl, R_2=OH .

4a-4j

4a: R_1=H, R_3=H;
4b: R_1=6-Cl, R_3=H;
4c: R_1=6-Br, R_3=H;
4d: R_1=6-I, R_3=H;
4e: R_1=H, R_3=Cl;
4f: R_1=H, R_3=CH_3;
4g: R_1=H, R_3=Ph;
4h: R_1=6,8-Cl_2, R_3=H;
4i: R_1=6,8-Br_2, R_3=H;
4j: R_1=6-Cl, R_3=Cl .

1a-1j

1a: R_1=H, R_3=H;
1b: R_1=6-Cl, R_3=H;
1c: R_1=6-Br, R_3=H;
1d: R_1=6-I, R_3=H;
1e: R_1=H, R_3=Cl;
1f: R_1=H, R_3=CH_3;
1g: R_1=H, R_3=Ph;
1h: R_1=6,8-Cl_2, R_3=H;
1i: R_1=6,8-Br_2, R_3=H;
1j: R_1=6-Cl, R_3=Cl .

Table 1 *Inhibition effect of compound **1a-1j** against nine kinds of phytopathogenic fungi in vitro*

Compound	Inhibitory ratio (%)[a]								
	G. zeae	*F. oxysporum*	*C. mandshurica*	*R. solani*	*T. cucumeris*	*S. sclerotiorum*	*B. cinerea*	*P. infestans*	*C. gloeosporioides*
1a	42.4 ± 1.08[b]	22.1 ± 1.13[b]	18.1 ± 1.55[b]	21.5 ± 1.34[b]	34.2 ± 1.58[b]	30.4 ± 1.01[b]	39.4 ± 0.82[b]	21.8 ± 1.00[b]	29.7 ± 0.92[b]
1b	96.3 ± 1.15[b]	51.3 ± 0.99[b]	64.8 ± 1.08[b]	78.2 ± 1.14[b]	50.4 ± 1.30[b]	43.6 ± 0.91[b]	32.3 ± 1.11[b]	59.4 ± 0.98[b]	41.8 ± 1.18[b]
1c	76.3 ± 0.98[b]	47.4 ± 0.94[b]	42.0 ± 1.22[b]	49.4 ± 0.86[b]	51.5 ± 1.34[b]	36.3 ± 0.87[b]	30.1 ± 1.14[b]	48.2 ± 0.99[b]	34.8 ± 1.21[b]
1d	62.9 ± 1.58[b]	40.8 ± 1.52[b]	43.6 ± 1.63[b]	43.2 ± 1.70[b]	32.3 ± 1.73[b]	34.0 ± 0.96[b]	22.7 ± 1.04[b]	42.5 ± 1.60[b]	21.7 ± 1.07[b]
1e	39.4 ± 1.64[b]	22.7 ± 1.12[b]	13.2 ± 1.75[b]	11.7 ± 0.87[b]	14.6 ± 1.92[b]	24.1 ± 1.00[b]	22.4 ± 1.10[b]	20.7 ± 1.54[b]	19.7 ± 1.06[b]
1f	21.2 ± 0.98[b]	18.7 ± 1.02[b]	24.1 ± 1.28[b]	28.7 ± 0.85[b]	25.7 ± 1.04[b]	NT	NT	NT	NT
1g	31.9 ± 0.99[b]	11.2 ± 0.94[b]	16.8 ± 1.50[b]	13.5 ± 1.25[b]	11.2 ± 1.83[b]	NT	NT	NT	NT
1h	83.7 ± 1.32[b]	57.8 ± 1.46[b]	51.5 ± 0.91[b]	44.1 ± 1.10[b]	42.0 ± 1.53[b]	40.5 ± 0.97[b]	30.7 ± 1.01[b]	50.7 ± 0.99[b]	38.1 ± 1.08[b]
1i	52.9 ± 1.02[b]	40.8 ± 1.22[b]	33.4 ± 1.03[b]	23.2 ± 1.55[b]	22.7 ± 1.08[b]	30.4 ± 0.98[b]	21.7 ± 1.54[b]	29.8 ± 1.75[b]	25.6 ± 1.58[b]
1j	86.1 ± 1.38[b]	37.2 ± 0.92[b]	46.8 ± 1.52[b]	49.4 ± 0.86[b]	69.5 ± 1.66[b]	NT	NT	NT	NT
Hymexazol[c]	53.7 ± 1.03[b]	52.1 ± 0.97[b]	52.0 ± 1.12[b]	52.1 ± 6.10[b]	56.3 ± 0.90[b]	51.9 ± 1.20[b]	55.0 ± 1.01[b]	50.3 ± 6.30[b]	50.6 ± 1.50[b]

Note: [a] Average of three replicates. [b] Compared with DMSO control, Hymexazole and 1a-1j treatment showed statistically significant inhibition ($P < 0.05$). [c] Positive control. [d] NT mean not tested.

1j showed considerable antifungal activities for the above bacterial cell lines at 50 μg/mL concentration *in vitro,* compared with the DMSO negative control. Furthermore, compared with the commercial antifungal drugs Hymexazol (a small molecular-targeted antifungal drug, 5-methylisoxazol-3-ol), **1b** showed better antifungal effects on corresponding cell lines at 50 μg/mL for most of the tests in bacteria (**Table 1**). The compounds **1b, 1c, 1d, 1h, 1i** and **1j** at 50μg/mL inhibited the growth of *G. zeae* at 96.3%, 76.3%, 62.9%, 83.7%, 52.9% and 86.1%, respectively. The compounds **1b** and **1h** at 50 μg/mL inhibited the growth of *F. oxysporum* and *C. mandshurica* at 51.3%, 64.8% and 57.8%, 51.5%, respectively. The compounds **1b** at 50μg/mL inhibited the growth of *R. solani, T. cucumeris* and *P. infestans* at 78.2%, 50.4% and 59.4%, respectively. There are better or a little higher than that of Hymexozole against the phytopathogenic fungi cell lines. Further bioassays disclosed that compounds **1b, 1c, 1d, 1h, 1i** and **1j** showed remarkable inhibitory effect on nine kinds of plant pathogenic fungi with **1b** showing the best result. When R_1 is 6-Cl or 6,8-2Cl atom, the inhibition is better than that R_1 is 6-Br or 6,8-2Br atom against nine kinds of phytopathogenic fungi *in vitro.* Title compounds containing-chlorine atoms of the antifungal activities were stronger than the activities of the compounds containing-bromine atoms, stronger than the activities of the compounds containing-iodine atoms, such as **1b, 1c, 1d** and **1h**, **1i, 1j**. The EC_{50} of **1b** on *G. zeae, F. oxysporum, C. mandshurica, R. solani, T. cucumeris, S. sclerotiorum, B. cinerea, P. infestans* and *C. gloeosporioides* were 4.68 μg/mL, 30.06 μg/mL, 20.42 μg/mL, 16.59 μg/mL, 46.77 μg/mL, 12.88 μg/mL, 30.9 μg/mL, 20.89 μg/mL and 25.12 μg/mL, respectively. Compound **1b** had more potent antifungal activities against most of the tested fungi and showed a broad-spectrum bioactivity (**Table 2**). These result suggested that **1b** will be a potential antifungal agent.

Table 2 *Toxicity of compound **1b** on nine kinds of phytopathogenic fungi in vitro*

Compound	Fungi	Toxic regression equation[a]	EC_{50}(μg/mL)[a]	r
Hymexazole[b]	*G. zeae*	Y=1.92x+2.27	26.46±7.1[c]	0.969
	F. oxysporum	Y=0.87x+3.84	21.41±9.3[c]	0.961
	C. mandshurica	Y=1.05x+3.46	29.13±7.6[c]	0.994
	R. solani	Y=2.73x+1.33	52.14±6.1[c]	0.995
	T. cucumeris	Y=0.95x+3.48	40.42±9.7[c]	0.965
	S. sclerotiorum	Y=3.48x+2.57	5.12±4.5[c]	0.931
	B. cinerea	Y=3.55x+2.63	4.63±3.9[c]	0.926
	P. infestans	Y=1.60x+2.76	25.13±9.3[c]	0.941
	C. gloeosporioides	Y=0.91x+3.91	15.85±8.2[c]	0.983
1b	*G. zeae*	Y=1.23x+4.18	4.68±5.3[c]	0.989
	F. oxysporum	Y=1.63x+2.59	30.06±6.7[c]	0.989
	C. mandshurica	Y=1.58x+2.93	20.42±5.9[c]	0.996
	R. solani	Y=1.66x+2.97	16.59±7.6[c]	0.984
	T. cucumeris	Y=1.12x+3.13	46.77±8.5[c]	0.996
	S. sclerotiorum	Y=2.58x+2.13	12.88±7.6[c]	0.988
	B. cinerea	Y=1.35x+2.99	30.9±6.4[c]	0.969
	P. infestans	Y=1.43x+3.11	20.89±6.9[c]	0.956
	C. gloeosporioides	Y=2.31x+2.03	25.12±7.6[c]	0.991

Note: [a] Average of three replicates. [b] Positive control. [c] Compared with acetone control, Hymexazole and 1b treatment showed statistically significant inhibition ($P < 0.05$).

CONCLUSION

A series of biquinazoline diselenide compounds was prepared with substituted 4-chloroquinazoline and sodium diselenide. Based on all findings, we concluded that the title compounds possessed wide-spectrum antifungal activities in *G. zeae, F. oxysporum, C. mandshurica, R. solani, T. cucumeris, S. sclerotiorum, B. cinerea, P. infestans* and *C. gloeosporioides* cell lines. Furthermore, compared with the commercial antifungal drugs hymexazole, **1b** also exerted better antifungal effects on the most corresponding cell lines at 50 μg/mL.

EXPERIMENTAL

General

All melting points of the products were determined on a MP120 digital melting point tester (Jinan Haineng Instruments, Ltd. Co., China) and are not corrected. The infrared spectra were recorded on a MAGANA-IR550 (series II) spectrometer in KBr disks. ^{1}H and ^{13}C-NMR spectra were recorded on a spectrometer BRUKER AVANCE III 600 MHz (600 and 150 MHz respectively) at room temperature in DMSO-d_6 using TMS as internal standard. Elemental analysis was performed by an Elementar Vario EL III CHN analyzer. The mass spectra were taken on a Agilent 6210 spectrometer.

The following compounds were prepared as described in the literature. *4-chloroquinazoline* (**4a**): white needle crystal, yield 55%, mp 94-95 °C (mp 96.5-97.5 °C [21]); *4,6-dichloroquinazoline* (**4b**): white solid, yield 63%, mp 152-154 °C (mp 154-155 °C [22]); 6-bromo-*4-chloroquinazoline* (**4c**): yellowish solid, yield 34%, mp 162-164 °C (mp 164-166 °C [23]); *4-chloro-6-*iodo*quinazoline* (**4d**): orange-yellow solid, yield 33%, mp 188-191 °C (mp 193-195°C [24]); *2,4-dichloro quinazoline* (**4e**)*:* yield 80%, mp 118-121 °C (mp 119.5 °C [25])*; 4-chloro-2-methylquinazoline* (**4f**)*:* yield 19%, mp 98.9-101.3 °C (mp 86-88 °C [26])*; 4-chloro-2-phenylquinazoline* (**4g**)*:* yellowish solid, yield 87%, mp 127.0-128.0 °C (mp 124 °C [27])*; 4,6,8-trichloroquinazoline* (**4h**)*:* yellowwish solid, yield 15%, mp 145.5-147.5 °C (mp 139-140 °C [28])*; 6,8-di*bromo-*4-chloroquinazoline* (**4i**): orange-yellow solid, yield 67%, mp 159.0-159.3 °C (mp 189-190 °C [24]); 2,*4,6-trichloroquinazoline* (**4j**)*:* yellowwish solid, yield 76%, mp 121-124 °C (mp 131 °C [29]). All the other reagents used in the experiment were analytical reagents without any modification.

General procedure for preparation biquinazolin-4-yl diselenide compounds 1a-1j

4-Chloroquinazoline or substituted 4-chloroquinazoline (5.0 mmol) was added to an ethanolic sodium diselenide solution 0.51 g (2.5 mmol) in 1 h. The solution was heated with reflux for 8–24 h, and reaction completion was monitored by TLC. After cooling and acidification using glacial acetic acid (pH 5), the solvents were removed *in vacuo* and recrystallized from DMF-H_2O to give the desired products **1a–1j**.

1,2-bis(quinazolin-4-yl)diselane **(1a**): orange-red solid, yield 44%, mp 220.7-222.0 °C. IR spectrum (thin layer), *ν*, cm^{-1}: 3140.8, 3055.6 (Ar-H), 1617.2-1466.4 (quinazoline skeleton). ^{1}H NMR spectrum (600 MHz, DMSO-d_6), *δ*, ppm (*J*, Hz): 7.66 (2H, s, H-2, 2' Ar), 7.76 (2H, d, *J* = 8.4, H-8, 8' Ar), 7.99 (2H, d, *J* = 8.4, H-5, 5' Ar), 8.21 (2H, t, *J* = 7.8, H-6, 6' Ar), 8.61 (2H, t, *J* = 7.8, H-7, 7' Ar). ^{13}C NMR spectrum (150 MHz, DMSO-d_6), *δ*, ppm (*J*, Hz): 127.6 (2C, C-5, 5' Ar), 129.5 (2C, C-6, 6' Ar), 132.4 (2C, C-8, 8' Ar), 136.3 (2C, C-7, 7' Ar), 143.9 (2C, C-10, 10' Ar), 144.7 (2C, C-9, 9' Ar), 154.2 (2C, C-2, 2' Ar), 162.8 (2C, C-4, 4' Ar). Mass spectrum (EI, 70 eV), *m/z* (I_{rel}, %): 420.0 $[M+2]^+$ (56), 417.9 $[M]^+$ (48), 327.7 $[M-C_6H_4N]^+$ (100), 301.7 $[M-C_6H_4N-CN]^+$ (33), 274.8 $[M-C_6H_4N-2CN]^+$ (88), 207.4 $[M-H-C_8H_5N_2Se]^+$ (80), 120.2 $[M-C_8H_5N_2Se-C_6H_4N]^+$ (22). Anal. calcd for $C_{16}H_{10}N_4Se_2$: C 46.17, H 2.42, N 13.46; found C 46.42, H 2.53, N 13.31.

1,2-bis(6-chloroquinazolin-4-yl)diselane (1b): orange-red solid, yield 29%, mp 255.2-257.9 °C. IR spectrum (thin layer), *ν*, cm^{-1}: 3083.3 (Ar-H), 1615.4-1450.9 (quinazoline skeleton), 647.7 (C-Cl). ^{1}H NMR spectrum (600 MHz, DMSO-d_6), *δ*, ppm (*J*, Hz): 7.78 (2H, d, *J* = 8.4, H-7, 7' Ar), 8.00 (2H, d, *J* = 8.4, H-8, 8' Ar), 8.20 (2H, s, H-5, 5' Ar), 8.55 (2H, s, H-2, 2' Ar). ^{13}C NMR spectrum (150 MHz, DMSO-d_6), *δ*, ppm (*J*, Hz): 130.9 (2C, C-5, 5' Ar), 131.3 (2C, C-10, 10' Ar), 133.6 (2C, C-8, 8' Ar), 133.9 (2C, C-7, 7' Ar), 136.1 (2C, C-6, 6' Ar), 142.6 (2C, C-9, 9' Ar), 145.2 (2C, C-2, 2' Ar), 186.9 (2C, C-4, 4' Ar). Anal. calcd for $C_{16}H_8Cl_2N_4Se_2$: C 39.62, H 1.66, N 11.55; found C 39.50, H 1.45, N 11.38.

1,2-bis(6-bromoquinazolin-4-yl)diselane (1c): orange-red solid, yield 41%, mp 225.9-227.3 °C. IR spectrum (thin layer), *ν*, cm^{-1}: 3017.6 (Ar-H), 1617.4-1454.8 (quinazoline skeleton), 559.1 (C-Br). ^{1}H NMR spectrum (600 MHz, DMSO-d_6), *δ*, ppm (*J*, Hz): 7.71 (2H, d, *J* = 9.0, H-8, 8' Ar), 8.12 (2H, dd, $J_{7,8}$ = 9.0, $J_{5,7}$ = 1.8, H-7, 7' Ar), 8.22 (2H, s, H-2, 2' Ar), 8.71 (2H, d, *J* = 1.8, H-5, 5' Ar). ^{13}C NMR spectrum (150 MHz, DMSO-d_6), *δ*, ppm (*J*, Hz): 122.4 (2C, C-6, 6' Ar), 131.4 (2C, C-10, 10' Ar), 133.9 (2C, C-5, 5' Ar), 134.1 (2C, C-8, 8' Ar), 138.8 (2C, C-7, 7' Ar), 142.9 (2C, C-9, 9' Ar), 145.3 (2C, C-2, 2' Ar), 186.5 (2C, C-4, 4' Ar). Anal. calcd for $C_{16}H_8Br_2N_4Se_2$: C 33.48, H 1.40, N 9.76; found C 33.25, H 1.28, N 9.98.

1,2-bis(6-iodoquinazolin-4-yl)diselane (1d): orange-red solid, yield 29%, mp 225.9-227.3 °C. IR spectrum (thin layer), *ν*, cm^{-1}: 3013.1 (Ar-H), 1615.7-1450.7 (quinazoline skeleton), 490.0 (C-I). ^{1}H NMR spectrum (600 MHz, DMSO-d_6), *δ*, ppm (*J*, Hz): 7.53 (2H, d, *J* = 8.4, H-8, 8' Ar), 8.20 (2H, s, H-5, 5' Ar), 8.25 (2H, d, *J* = 7.8, H-7, 7' Ar), 8.91 (2H, s, H-2, 2' Ar). ^{13}C NMR spectrum (150 MHz, DMSO-d_6), *δ*, ppm (*J*, Hz): 95.6 (2C, C-6, 6' Ar), 131.0 (2C, C-10, 10' Ar), 134.2 (2C, C-5, 5' Ar), 140.4 (2C, C-8, 8' Ar), 143.2 (2C, C-7, 7' Ar), 144.3 (2C, C-9, 9' Ar), 145.3 (2C, C-2, 2' Ar), 186.5 (2C, C-4, 4' Ar). Anal. calcd for $C_{16}H_8I_2N_4Se_2$: C 28.77, H 1.21, N 8.39; found C 28.64, H 1.09, N 8.55.

1,2-bis(2-chloroquinazolin-4-yl)diselane (1e): yellow-green solid, yield 10%, mp 134.2-136.0 °C. IR spectrum (thin layer), *ν*, cm^{-1}: 3079.0 (Ar-H), 1682.2-1469.2 (quinazoline skeleton). ^{1}H NMR spectrum (600 MHz, DMSO-d_6), *δ*, ppm (*J*, Hz): 7.18 (2H, t, *J* =7.8, H-6, 6' Ar), 7.38 (2H, t, *J* = 7.8, H-7, 7' Ar), 7.46 (2H, d, *J* =7.8, H-5, 5' Ar), 7.89 (2H, d, *J* = 7.8, H-8, 8' Ar). ^{13}C NMR spectrum (150 MHz, DMSO-d_6), *δ*, ppm (*J*, Hz): 114.8 (2C, C-10, 10' Ar), 116.6 (2C, C-5, 5' Ar), 122.8 (2C, H-8, 8' Ar), 127.3 (2C, C-6, 6' Ar), 135.4 (2C, C-7, 7' Ar), 141.0 (2C, H-9, 9' Ar), 159.3 (2C, C-2, 2' Ar), 172.5 (2C, C-4, 4' Ar). Anal. calcd for $C_{16}H_8Cl_2N_4Se_2$: C 39.62, H 1.66, N 11.55; found C 39.66, H 1.51, N 11.44.

1,2-bis(2-methylquinazolin-4-yl)diselane (1f): nacarat solid, yield 6%, mp 135.4-137.5 °C. IR spectrum (thin layer), *ν*, cm^{-1}: 3074.7 (Ar-H), 2924.7 (ν_{asCH3}), 2854.8 (ν_{sCH3}), 1684.2-1468.1 (quinazoline skeleton). ^{1}H NMR spectrum (600 MHz, DMSO-d_6), *δ*, ppm (*J*,

Hz): 3.34 (6H, s, $2CH_3$), 7.65 (2H, t, *J* =7.8, H-6, 6' Ar), 7.84 (2H, d, *J* =7.8, H-5, 5' Ar), 7.89 (2H, t, *J* =7.8, H-7, 7' Ar), 8.19 (2H, d, *J* =7.8, H-8, 8' Ar). ^{13}C NMR spectrum (150 MHz, DMSO-d_6), *δ*, ppm (*J*, Hz): 24.8 (2C, $2CH_3$), 123.4 (2C, C-10, 10' Ar), 126.5 (2C, C-5, 5' Ar), 128.9 (2C, C-6, 6' Ar), 129.1 (2C, C-8, 8' Ar), 135.3 (2C, C-7, 7' Ar), 147.7 (2C, C-9, 9' Ar), 160.6 (2C, C-4, 4' Ar), 161.4 (2C, C-2, 2' Ar). Anal. calcd for $C_{18}H_{14}N_4Se_2$: C 48.66, H 3.18, N 12.61; found C 48.38, H 2.95, N 12.48.

1,2-bis(2-phenylquinazolin-4-yl)diselane (1g): orange solid, yield 12%, mp 235.1-238.1 °C. IR spectrum (thin layer), *ν*, cm^{-1}: 3066.7 (Ar-H), 1631.9-1455.4 (quinazoline skeleton). ^{1}H NMR spectrum (600 MHz, DMSO-d_6), *δ*, ppm (*J*, Hz): 7.52-7.61 (8H, m, H-3, 3', 4, 4', 5, 5' Ph + H-6, 6' quinazoline), 7.75 (2H, d, *J* = 8.4, H-5, 5' Ar), 7.85 (2H, t, *J* = 8.4, H-7,7' Ar), 8.17-8.21 (6H, m, H-8, 8' quinazoline + H-2, 2', 6, 6' Ph). ^{13}C NMR spectrum (150 MHz, DMSO-d_6), *δ*, ppm (*J*, Hz): 121.5 (2C, C-10, 10' Ar), 126.3 (2C, C-5, 5' Ar), 127.1 (2C, C-6, 6' Ar), 128.0 (2C, C-8, 8' Ar), 128.2 (2C, C-4, 4' Ph), 129.1 (4C, C-2, 2', 6, 6' Ph), 131.8 (4C, C-3, 3', 5, 5' Ph), 133.2 (2C, C-7, 7' Ar), 135.1 (2C, C-1, 1' Ph), 149.2 (2C, C-9, 9' Ar), 152.8 (2C, C-4, 4' Ar), 162.7 (2C, C-2, 2' Ar). Anal. calcd for $C_{28}H_{18}N_4Se_2$: C 59.17, H 3.19, N 9.86; found C 59.38, H 2.99, N 9.73.

1,2-bis(6,8-dichloroquinazolin-4-yl)diselane (1h): orange solid, yield 31%, mp 261.5-263.8 °C. IR spectrum (thin layer), *ν*, cm^{-1}: 3082.9 (Ar-H), 1607.9-1470.9 (quinazoline skeleton), 656.6 (C-Cl). ^{1}H NMR spectrum (600 MHz, DMSO-d_6), *δ*, ppm (*J*, Hz): 8.10 (2H, s, H-5, 5' Ar), 8.27 (2H, s, H-7, 7' Ar), 8.90 (2H, s, H-2, 2' Ar). ^{13}C NMR spectrum (150 MHz, DMSO-d_6), *δ*, ppm (*J*, Hz): 118.1 (2C, C-5, 5' Ar), 122.0 (2C, C-10, 10' Ar), 131.2 (2C, C-7, 7' Ar), 133.4 (2C, C-6, 6' Ar), 134.3 (2C, C-8, 8' Ar), 155.8 (2C, C-9, 9' Ar), 166.1 (2C, C-2, 2' Ar), 173.0 (2C, C-4, 4' Ar). Anal. calcd for $C_{16}H_6Cl_4N_4Se_2$: C 34.69, H 1.09, N 10.11; found C 34.90, H 0.91, N 10.13.

1,2-bis(6,8-dibromoquinazolin-4-yl)diselane (1i): orange-red solid, yield 10%, mp 124.2-125.3 °C. IR spectrum (thin layer), *ν*, cm^{-1}: 3079.6 (Ar-H), 1600.2-1465.1 (quinazoline skeleton), 632.7 (C-Br). ^{1}H NMR spectrum (600 MHz, DMSO-d_6), *δ*, ppm (*J*, Hz): 8.28 (2H, s, H-5, 5' Ar), 8.51 (2H, s, H-7, 7' Ar), 8.92 (2H, s, H-2, 2' Ar). ^{13}C NMR spectrum (150 MHz, DMSO-d_6), *δ*, ppm (*J*, Hz): 118.5 (2C, C-6, 6' Ar), 120.1 (2C, C-10, 10' Ar), 124.4 (2C, C-5, 5' Ar), 125.8 (2C, C-8, 8' Ar), 139.9 (2C, C-7, 7' Ar), 147.4 (2C, C-9, 9' Ar), 155.9 (2C, C-2, 2' Ar), 165.9 (2C, C-4, 4' Ar). Anal. calcd for $C_{16}H_6Br_4N_4Se_2$: C 26.26, H 0.83, N 7.66; found C 26.11, H 0.98, N 7.50.

1,2-bis(2,6-dichloroquinazolin-4-yl)diselane (1j): pale yellow solid, yield 18 %, mp 133.2-135.5 °C. IR spectrum (thin layer), *ν*, cm^{-1}: 3071.8 (Ar-H), 1694.1-1464.6 (quinazoline skeleton), 619.4 (C-Cl). ^{1}H NMR spectrum (600 MHz, DMSO-d_6), *δ*, ppm (*J*, Hz): 7.67 (2H, d, *J* = 8.4, H-7, 7' Ar), 7.78 (2H, d, *J* =8.4, H-8, 8' Ar), 7.81 (2H, s, H-5, 5' Ar). ^{13}C NMR spectrum (150 MHz, DMSO-d_6), *δ*, ppm (*J*, Hz): 118.0 (2C, C-10, 10' Ar), 118.9 (2C, C-5, 5' Ar), 126.4 (2C, C-8, 8' Ar), 129.4 (2C, C-7, 7' Ar), 135.9 (2C, C-6, 6' Ar), 150.5 (2C, C-9, 9' Ar), 162.2 (2C, C-2, 2' Ar), 172.9 (2C, C-4, 4' Ar). Anal. calcd for $C_{16}H_6Cl_4N_4Se_2$: C 34.69, H 1.09, N 10.11; found C 34.52, H 1.11, N 9.89.

Antifungal assay:

The antifungal activities of compounds **1a–1j** were tested against *Gibberella zeae*, *Fusarium oxysporum*, *Cytospora mandshurica*, *Rhizoctonia solani*, *Thanatephorus cucumeris*, *Sclerotina sclerotiorum*, *Botrytis cinerea*, *Phytophthora infestans* and *Colletotrichum gloeosporioides* by the mycelium growth inhibition method [30]. Compounds **1a–1j** were dissolved in DMSO before mixing with 90 mL of potato dextrose agar (PDA). The final concentration of compounds **1a–1j** in the medium was 50 μg/mL. All kinds of fungi were incubated in PDA at 27 ± 1 °C for 4 days to obtain new mycelia for the antifungal assay. Then, mycelium dishes approximately 4 mm in diameter were cut from the culture medium, and one of them was picked up with a sterilized inoculation needle and inoculated in the center of the PDA plate aseptically. The inoculated plates were incubated at 27 ± 1 °C for 5 days. DMSO in sterile distilled water served as a control, whereas hymexazole served as a positive control. For each treatment, three replicates were conducted. The radial growth of fungal colonies was measured and the data were statistically analyzed. The inhibition effects of the tested compound *in vitro* on these fungi were calculated by the formula $I(\%) = [(C - T)/ (C - 0.4)] \times 100$, where *C* and *T* represent the diameters of fungus growth on untreated and treated PDA, and *I* is the inhibition rate. The EC_{50} values were estimated statistically by Probit analysis with the Probit package of SPSS 11.5 software using a personal computer [31]. The average EC_{50} (μg/mL) was taken (effective dose for 50% inhibition) from at least three separate analyses for the inhibition of growth using the Basic LD_{50} program version 1.1. The inhibition effects of compounds **1a–1j** are shown in **Table 1**. The toxicities of compound **1b** are shown in **Table 2**.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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