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Synthesis and antifungal activity of novel *s*-substituted 6-fluoro-4-alkyl(aryl)thioquinazoline derivatives

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Abstract—6-Fluoro-4-quinazolinol is prepared by the cyclization reaction of 2-amino-5-fluorobenzoic acid and formamide. The resulting thiol obtained by treatment of hydroxyl group with phosphorus (V) sulfide is converted under phase transfer condition to 4-substituted 4-alkylthio-6-fluoroquinazoline derivatives by reaction with halide. The structures of the compounds are confirmed by elemental analysis, IR, and ^{1}H NMR. Title compounds **3a**, **3g**, and **3h** are found to possess good antifungal activities. Using the mycelial growth rate method in the laboratory, the mechanism of action of **3g** against *Fusarium oxysporum* in vitro is studied. The results indicate that **3a**, **3g**, and **3h** have high inhibitory effect on the growth of most of the fungi with EC_{50} values ranging from 8.3 to 64.2 μg/mL. After treating *F. oxysporum* with compound **3g** at 100 μg/mL, only 6.5% of its spore bourgeoned. The permeability of the cell membrane increases along with the malformation of the hypha and condensation of its endosome. After treatment with compound **3g** at 100 μg/mL within 12 h, the mycelial reducing sugar, D-GlcNAc, content and chitinase activity decline, but the soluble protein content shows no obvious change.

1. Introduction

Fluorinated quinazoline derivatives represent one of the most active classes of compounds possessing a wide spectrum of biological activity. They are widely used in pharmaceuticals and agrochemicals.[1,2] A number of researches mention the utility of fluorinated quinazolines as important fungicide,[3] herbicide,[4] and antitumor agent.[5] Thus, their synthesis has been of great interest in the elaboration of biologically active heterocyclic compounds. Some high-bioactive compounds have been commercialized, for example, fluquinconazole fungicide for control of the agriculture disease.[6] We have been interested in the synthetic and agriculture chemistry of quinazoline derivatives with diversity at 4-position for many years. Recently, we reported the fungicidal activity of novel 3-alkylquinazolin-4-one derivatives, some of which were found to possess good fungicidal bioactivity.[7]

Prompted by these results and in an attempt to evaluate the modification of the fungicidal profile induced by the change of the substituents at the quinazoline ring, we designed and synthesized a series of 4-alkylthio-6-fluoroquinazolin derivatives with various substituents and measured their fungicidal activities. The synthetic route is shown in Scheme 1. The structures of **3** were firmly established by well- defined IR, ^{1}H NMR, and elemental analysis. Preliminary bioassay tests showed that some compounds possessed antifungal activity on three phytopathogenic fungi at 500 mg/L in vitro, but with a degree of variation. It was found that title compounds **3a**, **3g**, and **3h**, similar to a commercial product Hymexazol, displayed strong antifungal activities on hyphal growth of *G. zeae*, *Fusarium oxysporum*, and *C. mandshurica* in vitro. Many crops are easily infected by *F. oxysporum*, and the disease is hard to control. In our earlier studies, we found Hymexazol having higher antifungal activity compared to other commercial fungicides against *F. oxysporum*. Therefore, the mechanism of action of **3g** against *F. oxysporum* in vitro was studied with Hymexazol serving as the control. Some mechanistic aspects of compound **3g** on protein, metabolism, and cell structure are studied and presented in this paper.

Keywords: Quinazoline; Fluorine moiety; Thioether; Antifungal bioactivity; Mechanism of action.
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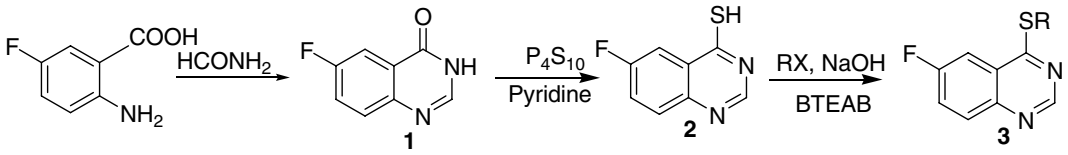

Scheme 1. Synthesis of compound **3**.

2. Chemistry

The synthetic route designed for the thioether analogues **3** of quinzoline is summarized in Scheme 1. The 2-amino-5-fluorobenzoic acid was converted to 6-fluoro-4-quinazolinol **1** by a cyclization procedure. Treatment of **1** with P_2S_5 in pyridine solution afforded compound **2**, 6-fluoro-4-quinazoline-thiol. Then, compound **2** was reacted with various halides under phase transfer catalysis condition to afford the title compounds **3a**–**3h**.

In order to optimize the reaction conditions, the synthesis of **3h** was carried out under various conditions. The effects of reaction time, reaction temperature, and phase transfer catalyst (PTC) on the reaction were investigated and the results are shown in Table 1. When no tribenzylethylammonium bromide (BTEAB) was used as catalyst, the reaction was relatively slow and the product was obtained in 38.0% when heated at 80–85 °C for 1 h (Table 1, entry 1). The yield of **3h** was increased to 89.0% under the same condition when the reaction was catalyzed by 0.06 equiv BTEAB (Table 1, entry 2). When the amount of BTEAB was varied as 2%, 4%, 8%, and 10%, **3h** could be obtained in 58.8%, 64.0%, 84.2%, and 86.7%, respectively (Table 1, entries 3–6). Using 6 mol% BTEAB as catalyst, the yield of **3h** increased from 79.9% to 89.0% when the reaction time was prolonged from 0.5 to 1 h at 80–85 °C (entries 2 and 7). When the reaction time was prolonged further to 2 h, little improvement in the yield (89.9%, entry 8) was observed, as compared to that of 1 h (89.0%, entry 2). As for the reaction temperature, it could be seen that the yield was relatively low when the reaction was carried out at 20–65 °C (Table 1, entries 9–11) than that at 80–85 °C.

Using the optimal condition, the best result was thus obtained when intermediate **2** was treated with 1 equiv of halides and 60 equiv of NaOH (20%, 10 mL) under PTC conditions (BTEAB, 0.06 equiv) with toluene as solvent (10 mL) and heated at 80–85 °C for 1 h. Under these reaction conditions, the thioetherification reaction proceeded smoothly, and products (**3a**–**3h**) were obtained in 70.0–89.0% yield (refer Section 5).

The structures of title compounds **3** were established on the basis of their spectroscopic data. They showed IR absorption bands at 3035–3045 cm^{-1} (Ar–H) and 1465–1591 cm^{-1} (skeleton vibration of aromatic ring). In the ^1H NMR spectra, the 2-H signal appeared as singlet in the range of 8.86–9.00 ppm. The chemical shift peaks of 7-H for 6-fluoro-4-alkylthioquinazoline derivatives were observed at 7.95–7.96 ppm as a quartet. The 5-H and 8-H signals were observed mostly as multiplets in the range of 7.56–7.80 ppm.

Table 1. Different reaction conditions for synthesis of **3h**

Entry[a]	Reaction time (h)	The amount of BTEAB (mol%)	Reaction temperature (°C)	Yield[b] (%)
1	1	—	80–85	38.8
2	1	6	80–85	89.0
3	1	2	80–85	58.8
4	1	4	80–85	64.0
5	1	8	80–85	84.2
6	1	10	80–85	86.7
7	0.5	6	80–85	79.9
8	2	6	80–85	89.9
9	1	6	20–25	10.1
10	1	6	40–45	29.3
11	1	6	60–65	68.0

[a] Reaction conditions, a mixture of 6-fluoroquinazolin-4-thiol (1 equiv) (**2**), 1-bromopropane (1 equiv), BTEAB (0.02–0.1 equiv), and 20% sodium hydroxide (60 equiv, 10 mL) in 10 mL of toluene was stirred at 20–85 °C for 0.5–2 h.

[b] Yields of isolated products.

3. Antifungal activity

The three fungi used in the fungicidal bioassay were *G. zeae*, *F. oxysporum*, and *C. mandshurica*. The results of preliminary bioassays were compared with that of a commercial agricultural fungicide, Hymexazol. As indicated in Table 2, most of the synthesized compounds showed certain antifungal activities against the tested fungi. The compounds **3a**, **3g**, **3h** at 500 μg/mL inhibited the growth of *G. zeae* at 100.0%, 100.0%, and 96.4%, respectively; *F. oxysporum* at 92.3%, 98.5%, and 89.3%, respectively; *C. mandshurica* at 96.9%, 100.0%, and 94.8%, respectively, which is a little higher than that of Hymexozole (100.0% against *G. zeae*, 91.3% against

Table 2. Inhibition[a] effect of 4-substituted 6-fluoro-4-alkylthioquinazoline derivatives at 500 μg/mL on phytopathogenic fungi

Compound	Inhibition (%)		
	G. zeae	*F. oxysporum*	*C. mandshurica*
3a	100.0 ± 2.9	92.3 ± 3.2	96.9 ± 3.9
3b	6.2 ± 4.9	5.3 ± 3.9	11.2 ± 6.7
3c	15.0 ± 2.9	18.9 ± 3.2	21.4 ± 8.1
3d	7.6 ± 3.6	5.9 ± 4.9	11.8 ± 6.0
3e	16.3 ± 8.1	21.9 ± 7.9	38.5 ± 9.9
3f	13.3 ± 4.6	20.3 ± 7.2	30.1 ± 9.0
3g	100.0 ± 1.1	98.5 ± 0.8	100.0 ± 0.9
3h	96.4 ± 0.9	89.3 ± 1.2	94.8 ± 0.9
Hymexazol	100.0 ± 3.2	91.3 ± 3.9	91.2 ± 4.0

[a] Average of three replicates.

Table 3. Toxicity of **3a**, **3g**, **3h**, and Hymexazol on nine kinds of pathogenic fungi

Compound	Fungi	Toxic regression equation[a]	EC_{50}[a] (μg/mL)	*r*
3a	*G. zeae*	$y = 2.38x + 1.27$	37.0 ± 6.8	0.997
	F. oxysporum	$y = 1.40x + 2.90$	32.2 ± 8.6	0.982
	C. mandshurica	$y = 1.43x + 3.05$	23.3 ± 7.9	0.984
	R. solani	$y = 2.29x + 1.18$	46.3 ± 6.2	0.991
	T. cucumeris	$y = 2.52x + 0.94$	40.6 ± 8.7	0.977
	P. infestans	$y = 1.78x + 1.96$	51.2 ± 8.9	0.960
	S. sclerotiorum	$y = 1.55x + 2.61$	35.2 ± 7.9	0.967
	B. cinerea	$y = 2.30x + 1.25$	42.4 ± 8.2	0.967
	C. gloeosporioides	$y = 2.54x + 1.62$	21.4 ± 8.1	0.967
3g	*G. zeae*	$y = 1.76x + 3.08$	12.4 ± 7.2	0.977
	F. oxysporum	$y = 1.51x + 3.10$	18.2 ± 6.6	0.988
	C. mandshurica	$y = 1.66x + 2.86$	19.2 ± 9.8	0.979
	R. solani	$y = 2.03x + 2.16$	24.9 ± 7.3	0.983
	T. cucumeris	$y = 1.81x + 2.30$	30.8 ± 9.4	0.962
	P. infestans	$y = 3.04x + 0.67$	26.8 ± 8.3	0.973
	S. sclerotiorum	$y = 3.27x + 1.54$	11.4 ± 9.2	0.940
	B. cinerea	$y = 1.42x + 3.70$	8.3 ± 7.8	0.960
	C. gloeosporioides	$y = 1.00x + 3.20$	64.2 ± 8.9	0.963
3h	*G. zeae*	$y = 1.41x + 2.99$	30.1 ± 6.6	0.982
	F. oxysporum	$y = 0.95x + 3.66$	25.1 ± 7.6	0.972
	C. mandshurica	$y = 1.26x + 3.22$	25.8 ± 8.7	0.966
	R. solani	$y = 1.43x + 2.91$	29.2 ± 9.9	0.966
	T. cucumeris	$y = 1.48x + 2.54$	46.2 ± 8.9	0.972
	P. infestans	$y = 2.18x + 1.89$	26.9 ± 8.1	0.998
	S. sclerotiorum	$y = 1.99x + 2.55$	17.1 ± 9.1	0.993
	B. cinerea	$y = 1.10x + 3.78$	13.0 ± 8.5	0.978
	C. gloeosporioides	$y = 1.62x + 2.40$	40.1 ± 8.8	0.943
Hymexazol	*G. zeae*	$y = 1.92x + 2.27$	26.4 ± 7.1	0.969
	F. oxysporum	$y = 1.05x + 3.46$	29.1 ± 7.6	0.994
	C. mandshurica	$y = 0.87x + 3.84$	21.4 ± 9.3	0.961
	R. solani	$y = 2.73x + 1.33$	52.1 ± 6.1	0.995
	T. cucumeris	$y = 0.95x + 3.48$	40.4 ± 9.7	0.965
	P. infestans	$y = 1.60x + 2.76$	25.1 ± 9.34	0.941
	S. sclerotiorum	$y = 3.48x + 2.57$	5.1 ± 4.5	0.931
	B. cinerea	$y = 3.55x + 2.63$	4.6 ± 3.9	0.926
	C. gloeosporioides	$y = 0.91x + 3.91$	15.8 ± 8.2	0.983

[a] Average of three replicates.

F. oxysporum, and 91.2% against *C. mandshurica* at 500 μg/mL) (Table 2). Further bioassays disclosed that compounds **3a**, **3g**, **3h** showed remarkable inhibitory effect on nine kinds of plant pathogenic fungi with **3g** showing the best result. The EC_{50} of **3g** on *G. zeae*, *F. oxysporum*, *C. mandshurica*, *R. solani*, *T. cucumeris*, *P. infestans*, *S. sclerotiorum*, *B. cinerea*, *C. gloeosporioides*, were 12.4 μg/mL, 18.2 μg/mL, 19.2 μg/mL, 24.9 μg/mL, 30.8 μg/mL, 26.8 μg/mL, 11.4 μg/mL, 8.3 μg/mL, and 64.2 μg/mL, respectively. Compound **3g** had more potent antifungal activities against most of the tested fungi and showed a broad-spectrum bioactivity (Table 3).

3.1. The morphology changes of hypha

The hypha of the control was slippy, vimineous and branched normally. The endosome of the cell distributed evenly. But when *F. oxysporum* was treated with 100 μg/mL of compound **3g**, most of its hypha became coarse and malformed. The cell of the hypha swelled and its endosome condensed, and formed blanks (Fig. 1).

3.2. Effect of compound 3g on sporule germination of *F. oxysporum*

It could be seen from Figure 2 that the sporule germination of *F. oxysporum* declined with the increase of the concentration. When the concentration was 60 μg/mL, the sporule germination was 68.7%, the inhibition was only 32.9%. While the concentration was over 60 μg/mL, the sporule germination declined remarkably, it was only 6.5% at 100 μg/mL.

3.3. Membrane permeability of *F. oxysporum*

After *F. oxysporum* was treated with compound **3g** (100 μg/mL), the relative permeability rate of the cell membrane was higher than the control. After 5 min, the relative permeability rate of the control was 6.0%, and for the treated one was 12.0%. When treated with Hymexazol, the observation was similar to that of the control. With longer treatment time, the relative permeability of the control rose gradually, but that of the one treated with compound **3g** and Hymexazol did not rise

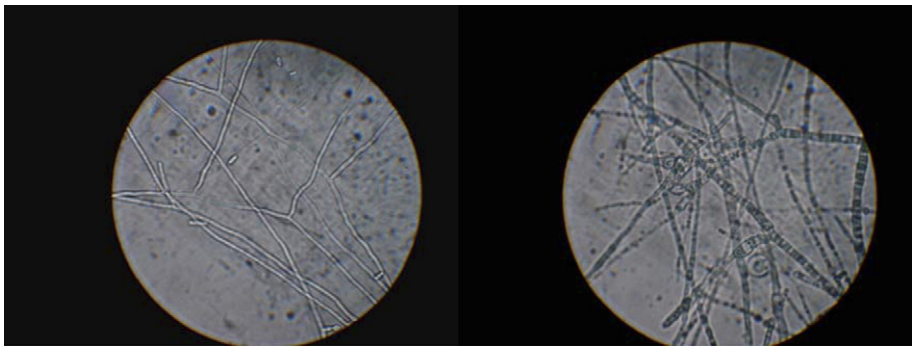

Figure 1. Microphotograph of the hyphal morphology of *Fusarium oxysporum* treated with compound **3g** (800×).

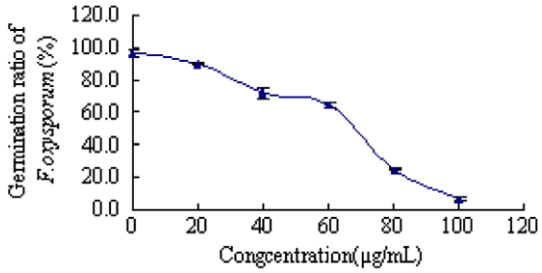

Figure 2. The effect of compound **3g** on sporule germination of *Fusarium oxysporum*.

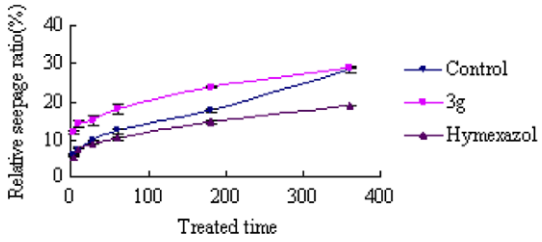

Figure 3. The effect of compound **3g** on membrane permeability of *Fusarium oxysporum*.

at the same rate. The result showed that when *F. oxysporum* was incubated with compound **3g**, the cell membrane was destroyed in short time, and the relative permeability of *F. oxysporum* treated with Hymexazol was lower than that of the control. The result may be attributed to the fact that Hymexazol site acting on *F. oxysporum* was not the cell membrane (Fig. 3).

3.4. Changes of mycelial reducing sugar content

After treatment with compound **3g**, mycelial reducing sugar content of *F. oxysporum* was lower than that of the control (Fig. 4). With prolonged treatment time, the reducing sugar content showed decreasing tendency. At 0.5 h, the mycelial reducing sugar content of the control was 1.27 mg/mL, but for the treated one, the value was only 1.02 mg/mL which was 19.8% lower than that of the control. After 6 h, the content of control started to rise, but that of the treated assumed decreasing tendency. At 12 h, the mycelial reducing sugar content of

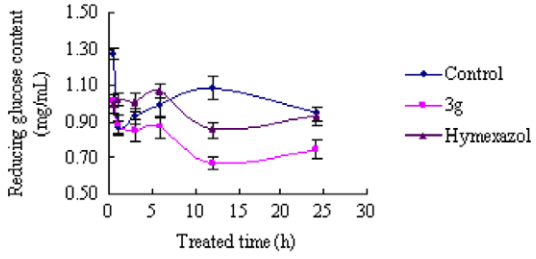

Figure 4. Changes of mycelial reducing sugar content.

the control, **3g**- and Hymexazol-treated *F. oxysparum* was 1.09 mg/mL, 0.67 mg/mL, and 0.85 mg/mL, respectively.

3.5. Changes of mycelial chitosan content

From Figure 5, we can see that when *F. oxysporum* was treated with compound **3g**, the mycelial chitosan content, namely the content of D-GlcNAc in the mycelial cell, started to fall at the beginning before showing a rising tendency. Initially, the observation was very similar to that of the control. After 1 h, the content of the D-GlcNAc was lower than that of the control. The content of D-GlcNAc was 0.0440 mg/mL when treated with compound **3g** at 6 h after inoculation, which was 6.1% lower than the control (control was 0.0469 mg/mL). After 6 h, while the content of control started to rise, that of the treated one began to fall. It could be inferred from Figure 5 that the content of D-GlcNAc of *F. oxysporum* treated with compound **3g** was lesser than that of the one commercial fungicide Hymexazol.

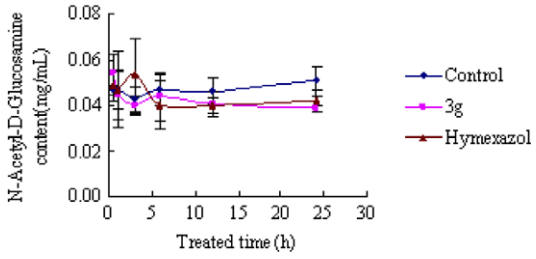

Figure 5. Changes of mycelial D-GlcNAc content.

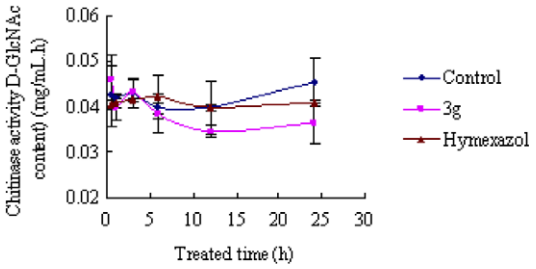

Figure 6. Changes of mycelial chitinase activity.

3.6. Changes of mycelial chitinase activity

Mycelial chitinase activity of *F. oxysporum* began to fall, then started to rise before showing a decreasing tendency at the end again. And the changes were similar to those of the D-GlcNAc content. With the increasing of time, the mycelial chitinase activity of the control rose gradually, and the treated one fell, 24 h after inoculation, the difference between control and that of the treated one reaching its highest value. The content of the D-GlcNAc that the chitinase had catalyzed in 1 h was 0.0455 mg/mL without treatment. When treated with compound **3g** and Hymexazol, the content was 0.0364 and 0.0411 mg/mL. The changes between Hymexazol-treated one and control was a little (Fig. 6).

3.7. Changes of mycelial soluble protein content

From Figure 7, we can see that when *F. oxysporum* was treated with compound **3g** for 0.5 h, the mycelial soluble protein content was 33.1% higher than that of the control. Half an hour later, the soluble protein content of *F. oxysporum* treated with compound **3g** was similar to that of the control. The value was lower than that of

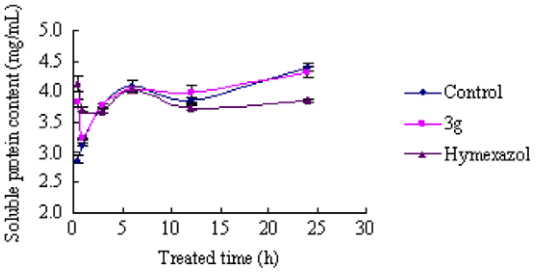

Figure 7. Changes of mycelial soluble protein content.

the control after being incubated with Hymexazol for 6 h. It should be noted that the reaction in the cell was very complicated. It is not safe to conclude at this stage that compound **3g** has no effect on the synthesis of the protein. The study requires further investigation.

4. Conclusion

In summary, the present method of formation of 4-substituted 6-fluoro-4-alkylthioquinazoline derivatives under phase transfer catalyst condition offers several advantages such as faster reaction rate, lesser by-products, and high yield. It was also found that title compounds **3a**, **3g**, and **3h** displayed good antifungal activity, especially compound **3g**, having a wide spectrum of bioactivity. The results showed that **3g** had high inhibitory effect on the growth of most of the fungi with EC_{50} values ranging from 8.3 to 64.2 μg/mL. After *F. oxysporum* was treated with compound **3g** at 100 μg/mL, the permeability of the cell membrane rose and the hypha became coarse, malformed, its endosome condensed and formed blanks, and 6.5% of its spore bourgeoned. After being treated with compound **3g** at 100 μg/mL within 12 h, chitinase activity, the content of mycelial reducing sugar and D-GlcNAc all declined. We can conclude that the membrane of cell may be destroyed by compound **3g**, and the ability of sugar absorption by the cell from the culture medium is depressed. From the changes of chitosan content and chitinase activity, we conclude that compound **3g** can inhibit the activity of chitinase in the cell of *F. oxysporum* and destroy the cell wall. But these were not obvious when *F. oxysporum* was treated with Hymexazol, perhaps due to the fact that cell structure was not the main site that Hymexazole acts on. In addition, the content of soluble protein was similar to that of the control when *F. oxysporum* was treated with compound **3g**, and it reduced to 87.8% of the control after being treated with Hymexazol for 24 h. These results indicate that compound **3g** had little effect on the content of soluble protein and Hymexazol caused a certain degree of disturbance on the synthesis of the protein. The biochemical action in the cell is very complicated. Although it is true that some work had been done, the precise way in which compound **3g** efficiently inhibits the growth of the hypha still remains to be ascertained. So, further investigation requires to be done in the future research (Fig. 8).

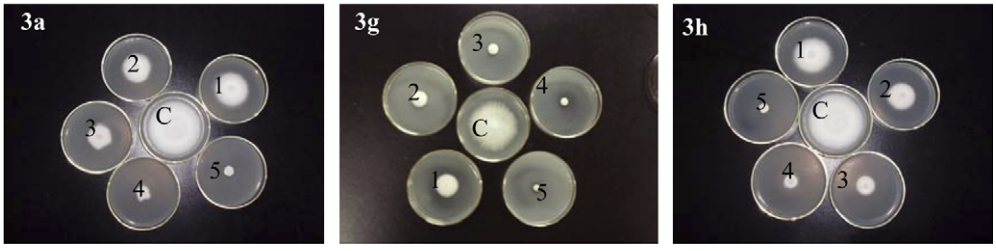

Figure 8. Effect of different concentrations of **3a**, **3g**, and **3h** on *the mycelial growth* of *Fusarium oxysporum* (6.25, 12.5, 25.0, 50.0 and 100 μg/mL). Key (μg/mL): 1, 6.25; 2, 12.5; 3, 25; 4,50; 5,100; and C, control (the radial growth of the smallest).

5. Experimental

5.1. Analysis and instruments

The melting points of the products were determined on a XT-4 binocular microscope (Beijing Tech Instrument Co., China) and are not corrected. The IR spectra were recorded on a Bruker VECTOR22 spectrometer in KBr disks. ^{1}H NMR spectra were recorded on a Varian-INOVA 400 MHz spectrometer in $CDCl_3$ at room temperature using TMS as an internal reference. Elemental analysis was performed on an Elementar Vario-III CHN analyzer. The reagents were all of analytical grade or chemically pure.

5.1.1. Preparation of 6-fluoro-4-quinazolinol (1). A mixture of formamide (5.4 g, 120 mmol) and 2-amino-5-fluorobenzoic acid (2.4 g, 15 mmol) was stirred at 135 °C for 7 h. The mixture was then poured into ice water (10 mL). The crude product was then filtered off and recrystallized from ethanol. Yield 53%, mp 258–261 °C.[8]

5.1.2. Preparation of 6-fluoro-4-quinazoline-thiol (2). P_2S_5 (10.8 g, 48 mmol) was added to a solution of 6-fluoro-4-quinazolinol (4.0 g, 24 mmol) in anhydrous pyridine (100 mL), and the mixture was heated at 90 °C for 2 h. The reaction mixture was then poured into ice water, and the resultant precipitate was dissolved in aqueous KOH (10%). Acidification of the solution with acetic acid afforded the product, which was filtered off and dried. Yield 95%, mp >300 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50–7.59 (m, 1H, 8-H of quinazoline), 7.66 (dd, 1H, J = 8.5, 2.2 Hz, H-5 of quinazoline), 7.93 (q, 1H, J = 5.5, 4.0 Hz, H-7 of quinazoline), 8.90 (s, 1H, H-2 of quinazoline), 10.52 (s, 1H, SH); Anal. Calcd for $C_8H_5FN_2S$: C, 53.32; H, 2.80; N, 15.55. Found: C, 53.10; H, 2.70; N, 15.43.

5.2. General procedure for the preparation of the title compounds (3a–3h)

A mixture of 6-fluoro-4-quinazoline-thiol (225 mg, 1.25 mmol), halides (1.25 mmol), and tribenzyl ethylammonium bromide (0.075 mmol) was dissolved in toluene (10 mL) and 20% aqueous potassium hydroxide (60.5 mmol, 10 mL). The solution was stirred for 1 h and then the organic layer was separated, washed with water, and dried over magnesium sulfate. After evaporation of solvent, the oily crude product was purified by preparative TLC with petroleum ether/ethyl acetate (1:1, v/v) as developing solvent to give title compounds **3**.

5.2.1. Data for 4-allylthio-6-fluoroquinazoline (3a). White crystal; mp, 62–64 °C; yield, 72.1%; IR (KBr) ν (cm^{-1}): 3040.2, 1558.3, 1543.1, 1490.1, 1336.7, 1290.5, 1180.4, 999.1, 912.3, 848.9, 837.1, 525.3; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.07 (d, 2H, SCH_2), 5.19–6.07 (m, 3H, $CH{=}CH_2$), 7.58–7.69 (m, 2H, 5, 8-H of quinazoline), 7.95–7.99 (q, 1H, J = 5.2, 4.0 Hz, 7-H of quinazoline), 8.97 (s, 1H, 2-H of quinazoline); Anal. Calcd for $C_{11}H_9FN_2S$: C, 59.98; H, 4.12; N, 12.72. Found: C, 59.71; H, 4.22; N, 12.63.

5.2.2. Data for 2-(6-fluoroquinazolin-4-ylthio)-1-(2,3,4-trimethoxyphenyl) ethanone (3b). White crystal; mp, 152–154 °C; yield, 70.5%; IR (KBr) ν (cm^{-1}): 3039.5, 1662.6, 1591.3, 1568.1, 1492.9, 1336.7, 1290.4, 1103.3, 999.1, 839.0, 688.6; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.92–4.12 (3s, 9H, $3CH_3O$), 4.88 (s,2H,CH_2), 6.78 (d, J = 8.8Hz, 1H, PhH), 7.59–7.80 (m, 3H, Ph–H and H-5, 8 of quinazoline), 7.95–7.99 (q, 1H, J = 5.2, 4.0 Hz, H-7 of quinazoline), 8.86 (s, 1H, 2-H of quinazoline); Anal. Calcd for $C_{19}H_{17}FN_2O_4S$: C, 58.75; H, 4.41; N, 7.21. Found: C,58.52; H, 4.53; N,7.14.

5.2.3. Data for 4-benzylthio-6-fluoroquinazoline (3c). White crystal; mp, 83–84 °C; yield, 73.8%; IR (KBr) ν (cm^{-1}): 3035.3, 1566.2, 1492.9, 1485.2, 1334.7, 1184.3, 914.3, 837.1, 698.2, 686.7, 526.6. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.64 (s, 2H, CH_2),7.26–7.47 (m, 5H, Ph–H) 7.56–7.66 (m, 2H, 5, 8-H of quinazoline), 7.95–7.98 (q, 1H, J = 5.2, 4.0 Hz, H-7 of quinazoline), 9.00 (s, 1H, 2-H of quinazoline); Anal. Calcd for $C_{15}H_{11}FN_2S$: C, 66.65; H, 4.10; N, 10.36. Found: C, 66.46; H, 4.20; N, 10.25.

5.2.4. Data for 4-(4-chlorobenzylthio)-6-fluoroquinazoline (3d). White crystal; mp, 115–117 °C; yield, 74.0%; IR (KBr) ν (cm^{-1}): 3045.5, 1559.2, 1492.5, 1398.7, 1325.4, 1243.2, 1190.4, 1080.3, 920.5, 880.3, 674.5. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.60 (s, 2H, CH_2),7.30 (d, J = 8.4 Hz, 2H, Ph–H), 7.42 (d, J = 8.4 Hz, 2H, Ph–H), 7.59–7.66 (m, 2H, 5, 8-H of quinazoline), 7.96–8.00 (q, 1H, J = 5.2, 3.6 Hz, H-7 of quinazoline), 8.99 (s, 1H, 2-H of quinazoline). Anal. Calcd for $C_{15}H_{10}ClFN_2S$: C, 59.11; H, 3.31; N, 9.19. Found: C, 59.58; H, 3.69; N, 9.36.

5.2.5. Data for 4-(2-chloro-5-pyridylmethylthio)-6-fluoroquinazoline (3e). White crystal; mp, 113.5–115.5 °C; yield, 88.0%; IR (KBr) ν (cm^{-1}): 3045.3, 1566.2, 1492.9, 1465.9, 1382.5, 1332.8, 1184.3, 1113.5, 950.2, 835.2; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.59 (s, 2H, CH_2), 7.29 (d, J = 8.4 Hz, 1H, pyridine–H),7.61–7.65 (m, 2H, 5, 8-H of quinazoline), 7.79 (d, J = 8.4 Hz, 1H, pyridine–H), 7.98–8.02 (q, 1H, J = 5.2, 4.8 Hz, H-7 of quinazoline), 8.54 (s, 1H, pyridine–H), 8.99 (s, 1H, 2-H of quinazoline); Anal. Calcd for $C_{14}H_9ClFN_3S$: C, 54.99; H, 2.97; N, 13.74. Found: C, 55.09; H, 3.06; N, 13.65.

5.2.6. Data for 4-(2-ethoxycarboxylmethylenethio)-6-fluoroquinazoline (3f). White crystal; mp, 119.5–122 °C; yield, 90.0%; IR (KBr) ν (cm^{-1}): 3042.5, 2980.5, 2810.2, 1743.7, 1489.1, 1365.6, 1334.7, 1305.8, 1186.2, 1165.0, 1003.0, 841.0, 688.6; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.31 (t, J = 7.2 Hz, 3H, CH_3), 4.17 (s, 2H, SCH_2), 4.26 (q, J = 6.8, 7.2 Hz, 2H, OCH_2), 7.61–7.71 (m, 2H, 5, 8-H of quinazoline), 7.98–8.02 (q, 1H, J = 5.2, 4.0 Hz, 7-H of quinazoline), 8.95 (s, 1H, 2-H of quinazoline); Anal. Calcd for $C_{12}H_{11}FN_2O_2S$: C, 54.12; H, 4.16; N, 10.52. Found: C, 54.22; H, 4.27; N, 10.52

5.2.7. Data for 4-ethylthio-6-fluoroquinazoline (3g). White crystal; mp, 39–41 °C; yield, 80.7%; IR (KBr) ν (cm^{-1}): 3040.2, 2966.5, 1566.2, 1541.1, 1492.9, 1336.7, 1290.5, 1180.4, 966; ^{1}H NMR (400 MHz, $CDCl_3$): δ

1.46 (t, $J = 7.5$ Hz, 3H, CH_3), 3.39 (q, $J = 7.5$ Hz, 2H, CH_2), 7.58–7.65 (m, 1H, 8-H of quinazoline), 7.68 (dd, $J = 8.6$, 2.3 Hz, H-5 of quinazoline), 7.95 (q, 1H, $J = 5.2$, 4.0 Hz, H-7 of quinazoline), 8.95 (s, 1H, H-2 of quinazoline); Anal. Calcd for $C_{10}H_9FN_2S$: C, 57.60; H, 4.32; N, 13.44. Found: C, 57.70; H, 4.20; N, 13.43.

5.2.8. Data for 4-*n*-propylthio-6-fluoroquinazoline (3h). White crystal; mp, 62–64 °C; yield, 89.0%; IR (KBr) ν (cm^{-1}): 3040.2, 2966.5, 1564.3, 1545.0, 1492.9, 1336.0, 1291.0, 1182.0. ^1H NMR (400 MHz, $CDCl_3$): δ 1.09 (t, $J = 7.5$ Hz, 3H, CH_3), 1.80–1.84 (m, 2H, CH_2), 3.35 (t, $J = 7.5$ Hz, 2H, SCH_2), 7.57–7.96 (m, 3H, 5, 7, 8-H of quinazoline), 8.94 (s, 1H, H-2 of quinazoline); Anal. Calcd for $C_{11}H_{11}FN_2S$: C, 59.38; H, 4.94; N, 12.60. Found: C, 59.21; H, 4.82; N, 12.53.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2007.03.037.

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