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Synthesis and Antifungal Bioactivities of 3-Alkylquinazolin- 4-one Derivatives

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Abstract: A simple, efficient, and general method has been developed for the synthesis of various 3-alkylquinazolin-4-one derivatives from quinazolin-4-one treated with alkyl bromides under phase transfer catalysis condition. The structures of the compounds were characterized by elemental analysis, IR, ^{1}H-NMR and ^{13}C-NMR spectra. Title compound 6-bromo-3-propylquinazolin-4-one (**3h**) was found to possess good antifungal activity.

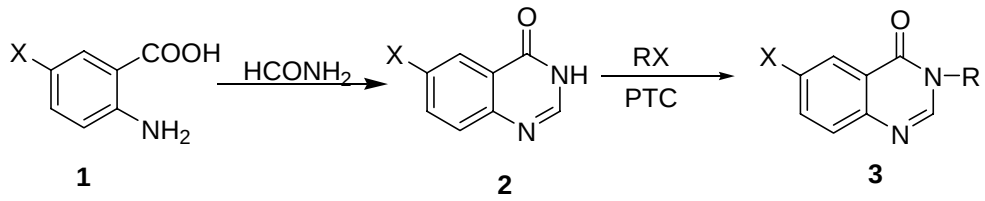
Keywords: Quinazolinone, Phase Transfer Catalyst, synthesis, antifungal activity

Introduction

A variety of the reports regarding synthetic studies of quinazolinone derivatives have been presented due to the chemical and biological interests to the quinazoline [1, 2]. Quinazoline compounds are widely used in agrochemicals as plant virucides [3], antifungal agents [4] and herbicides [5]. According to recent data, quinazoline nucleus has attracted the attention of medicinal chemists due to its well known anticancer activity, and many substituted quinazoline derivatives have recently earned great interest in chemotherapy as antitumor drugs [6, 7]. In order to find potential new plant fungicides and anticancer agents, we had designed and synthesized a series of

N-aryl-4-aminoquinazoline compounds, among which some compounds were found to possess moderate bioactivity [8]. In this report we designed and synthesized a series of 3-alkylquinazolin-4-one derivatives and investigated their bioactivities. The synthetic route was shown in Scheme 1. The structures of **3** were firmly established by well defined IR, ^{1}H-NMR, ^{13}C-NMR and elemental analysis. Preliminary bioassay tests showed that some compounds displayed antifungal activity against three fungi at 50 μg/mL *in vitro*, but with a degree of variation. It was found that title compound **3h** displayed strong *in vitro* antifungal activity on hyphal growth of *F. oxysporum*, *Valsa mali* and *Gibberella zeae*.

Scheme 1 Synthetic route to the title compounds.



1 **2** **3**

X= H, F, Cl, Br. R= Et, *n*-Pr, Allyl

Results and Discussion

In order to optimize the reaction conditions, the synthesis of **3e** was carried out under various conditions. The effects of KOH concentration, reaction time, reaction temperature, presence or absence of a phase transfer catalyst (PTC) on the reaction were investigated and the results are shown in Table 1. When no tetrabutylammonium bromide was used as PTC, the reaction was relatively slow and the product was obtained in 8.5 % refluxed at 88-90 °C for 1 h (Table 1, entry 5), while the use of the PTC obviously accelerated the reaction (Table 1, entries 1-4). While the yield of **3e** increased to 77.1 % also in 1 h when the reaction was catalyzed by 0.08 equiv Bu_4NBr (Table 2, entries 3 and 5). When the amount of Bu_4NBr increased from 3 % to 5 %, 8 % and 10 %, **3e** could be obtained in 38.8 % and 62.2 %, 77.1 % and 77.4 %, respectively (Table 1, entries 1-4). The effect of KOH concentration was also studied. When KOH concentration increased from 10 %, to 20 %, 30 % and 35 % with Bu_4NBr as catalyst, **3e** could be obtained in 48.5 %, 69.1 %, 77.1 % and 83.0 %, respectively (entries 6-7, 3, 8). Interestingly, lower yield of **3e** was obtained when KOH concentration increased from 35 % to 40 % (entries 8-9), which indicated that 35 % was the best KOH concentration. Using 8 mol% tetrabutylammonium bromide as catalyst, the yield of **3e** increased from 55.9 % to 83.0 % when the reaction time was prolonged from 0.5 to 1 h refluxed at 88-90 °C (entries 8, 14 and 15). When the reaction time was prolonged further to 2 h, tiny improvement (83.8 %, entry 13) was obtained, as compared to that of 1 h (83.0 %, entry 8). 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 10-12) than that at 88-90 °C (entry 8).

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

Entry [a]	Reaction time / h	KOH concentration / % (w/w)	The amount of Bu_4NBr / mol %	Reaction temperature / °C	Yield [b] / %
1	1	30	3	88-90	38.8
2	1	30	5	88-90	62.2
3	1	30	8	88-90	77.1
4	1	30	10	88-90	77.4
5	1	30	0	88-90	8.5
6	1	10	8	88-90	48.5
7	1	20	8	88-90	69.1
8	1	35	8	88-90	83.0
9	1	40	8	88-90	74.0
10	1	35	8	20-25	4.3
11	1	35	8	40-45	13.3
12	1	35	8	60-65	65.0
13	2	35	8	88-90	83.8
14	0.75	35	8	88-90	74.5
15	0. 5	35	8	88-90	55.9

[a] Reaction conditions: A mixture of quinazolin-4-one (1 equiv) (**2e**), 1-bromopropane (1 equiv), Bu_4NBr (0.03-0.1 equiv), 10-40 % potassium hydroxide (10 mL) in toluene (10 mL) was stirred at 20-90°C for 0.5-2 h.

[b] Yields of isolated products.

The effect of different organic phase was also investigated. When $CHCl_3$, benzene, ethyl atetate, and toluene was used, the yields of **3e** were 25.5 %, 45.2 %, 54.3 % and 83.0 %, respectively (Table 2). By using toluene as the organic phase, the **3e** synthesis was found to proceed smoothly in PTC condition at 88-90°C.

Table 2 Effect of different organic solvents on the synthesis of **3e**

Entry [a]	Reaction time / h	organic phase	The amount of solvent / mL	Yield [b] / %
1	1	$CHCl_3$	10	25.5
2	1	C_6H_6	10	45.2
3	1	CH_3COOEt	10	54.3
4	1	Toluene	10	83.0

[a] Reaction conditions: A mixture of quinazolin-4-one (1 mmol) (**2e**), 1-bromopropane (1.0 mmol), Bu_4NBr (0.08 mmol), 35 % potassium hydroxide (84 mmol, 10mL) in toluene (10 mL) was stirred at 88-90°C for 1 h.

[b] Yields of isolated products.

Using the optimized condition, the best result was obtained when intermediate **2** was treated with 1 equiv of alkyl halides and 84 equiv KOH (35%, 10 mL) under PTC conditions (Bu_4NBr, 0.08 equiv) with toluene as solvent (10 mL) refluxed at 88-90 °C for 1 h. Under these reaction conditions, the amination reaction proceeded smoothly, and the results are summarized in **Table 3**. Compounds **3e** and **3i** were prepared previously in yields of 41% and 33%, respectively [8], by the reaction of metallic derivatives of substituted or unsubstituted quinazolin-4-one with alkyl halides or dialkyl sulfate in ethanol solvent for 6-24 hrs.

Table 3. Yields of the title compounds **3**.[a]

Compd	**3a**	**3b**	**3c**	**3d**	**3e**	**3f**
X-	H	F	Cl	Br	H	F
R-	Et	Et	Et	Et	*n*-Pr	*n*-Pr
[b]Yields /%	79.5	74.5	74.5	77.0	83.0	92.2
Compd	**3g**	**3h**	**3i**	**3j**	**3k**	**3l**
X-	Cl	Br	H	F	Cl	Br
R-	*n*-Pr	*n*-Pr	allyl	allyl	allyl	allyl
[b]Yields /%	83.1	87.0	70.0	72.7	82.5	70.9

[a] All reactions were carried out in toluene (10 mL) at 88-90°C for 1 h under PTC conditions with KOH (84 equiv) used as base.

[b] Isolated yields.

The structures of title compounds **3** were established on the basis of their spectroscopic data. They showed IR absorption bands at 3049-3099 (Ar-H), 1664-1678 (C=O), and 1451-1613 cm^{-1} (skeleton vibration of aromatic ring). In the ^1H NMR spectra of quinazolinone derivatives, the 2-H signal appeared as a singlet in the 7.99-8.08 ppm range, while the 7-H peaks of 6-fluoro-quinazolin-4-one derivatives were observed at about 7.72-7.73 ppm as a quartet. The 8-H of 6-bromoquinazolin-4-one derivatives appear as a doublet at 7.57-7.60 ppm.

Antifungal activity bioassay

The antifungal bioassay results are given in Table 4. It could be seen that these newly synthesized 3-alkylquinazolin-4-one derivatives exhibit weak to good antifungal activities. At 50 μg/mL, compounds **3c**, **3h** and **3k** inhibited growth of *Gibberella zeae* at 55.0 %, 50.3 % and 49.1 % respectively. Compounds **3h**, **3c**, **3k**, **3d** and **3l** exhibited good activities on *Fusarium oxysporum* at 47.2 %, 37.5 %, 36.4 %, 33.3 %, 32.4 %, respectively, which is slightly lower than that of hymexazol (55.4 %). Compounds **3l**, **3k**, **3c** showed activities against *Valsa mali* at 30.4 %, 28.3 %, 24.4 %, respectively, which is little higher than *Hymexazol* (22.5 %). Compounds **3h** showed activities against *Valsa mali* at 40.9 %, which is obviously higher than *Hymexazol* (22.5 %).

Table 4. Inhibition effect of 3-alkylquinazolin-4-one derivatives on phytopathogenic fungi.

Compd (50 μg/mL)	*Fusarium oxysporum*	*Gibberella zeae*	*Valsa mali*
3a	17.9	17.6	8.7
3b	14.2	11.8	6.5
3c	37.5	55.0	24.4
3d	33.3	35.4	21.7
3e	21.2	17.3	16.9
3f	4.9	17.0	14.5
3g	20.4	5.5	15.9
3h	47.2	50.3	40.9
3i	15.3	19.9	0.9
3j	13.9	26.7	13.4
3k	36.4	49.1	28.3
3l	32.4	37.0	30.4
Hymexazol	55.4	50.4	22.5

Conclusions

In summary, the present new method of the formation of 3-alkylquinazolin-4-one derivatives under phase transfer catalyst condition offers several advantages: fast reaction rates, less by-products, and high yields. Where direct comparisons were possible our method was found to be superior to reported methods It was also found that title compound **3h** displayed good antifungal activity.

Acknowledgements

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Experimental

General

Unless otherwise indicated, all common reagents and solvents were used as obtained from commercial suppliers without further purification. Melting points were determined on a XT-4 binocular microscope (Beijing Tech Instrument Co., China) and were not corrected. The IR spectra were recorded on a Bruker VECTOR 22 spectrometer in KBr disks. ^{1}H-NMR and ^{13}C-NMR spectra (solvent $CDCl_3$) were recorded on a JEOL ECX 500 MHz spectrometer at room temperature using TMS as internal standard. Elemental analysis was performed by an Elementar Vario-III CHN analyzer. The following compounds were prepared as described in the literature: *quinazolin-4-one* (**2a**): white solid, yield 95.4%, m.p. 214~215°C (lit. [9], m.p. 215.5~216.5°C); *6-fluoroquinazolin-4-one* (**2b**):

white solid, yield 70.8%, m.p. 258-260 °C (lit. [10], m.p. 255-257 °C); *6-chloroquinazolin-4-one* (**2c**): white solid, yield 78.5%, m.p. 257-260 °C (lit. [11], m.p. 259-259.5 °C) and *6-bromoquinazolin-4-on*e (**2d**): white solid, yield 69.5 %, m.p. 264-267°C (lit. [12], m.p. 267-269 °C).

Preparation of 3-Alkylquinazolin-4-one Derivatives **3a-3l**

A mixture of quinazolin-4-one or 6-haloquinazolin-4-one (1.00 mmol), alkyl bromide (1.00 mmol) and tetrabutylammonium bromide (26 mg, 0.08 mmol) was dissolved in toluene (10 mL) and 35% aqueous potassium hydroxide (10 mL). The solution was stirred and refluxed for 1 h and then the organic layer was separated and washed with water. After evaporation of solvent, the crude product was purified by preparative TLC with petroleum ether/ethyl acetate (*V*/*V*=1:2) as developing solvent to give title compounds **3**.

3-Ethylquinazolin-4-one (**3a**). White crystals, yield 79.5%; m.p. 76.5~78.5 °C; (lit. [8], m.p. 99-101 °C, yield not reported). IR: 3049.2, 2960.5, 1674.2, 1612.5, 1562.3, 1471.7 cm^{-1}; ^{1}H-NMR: δ 8.32 (d, 1H, *J*=8.0Hz, quinazolinone H-5), 8.08 (s, 1H, quinazolinone H-2), 7.76-7.71 (m, 2H, quinazolinone H-6,8), 7.51 (t, 1H, *J*=6.9Hz, quinazolinone H-7), 4.08 (q, 2H, *J*=7.5Hz, CH_2), 1.43 (t, 3H, *J*=7.5Hz, CH_3); ^{13}C-NMR: δ 160.8 (quinazolinone C-4), 148.1 (quinazolinone C-2), 146.3 (quinazolinone C-9), 134.1 (quinazolinone C-7), 127.4 (quinazolinone C-5), 127.2 (quinazolinone C-6), 126.6 (quinazolinone C-10), 122.2 (quinazolinone C-8), 42.1 (CH_2), 14.9 (CH_3); *Anal.* Calc. for $C_{10}H_{10}N_2O$ (174.2): C, 68.95; H, 5.79; N, 16.08. Found: C, 68.80; H, 5.79; N, 16.18.

3-Ethyl-6-fluoroquinazolin-4-one (**3b**). White crystals, yield 74.5%; m.p. 94.5~96.5 °C; IR: 3058.6, 2974.2, 1674.2, 1626.0, 1606.7, 1487.1 cm^{-1}; ^{1}H-NMR: δ 8.05 (s, 1H, quinazolinone H-2), 7.94 (dd, 1H, *J*=8.6Hz, 2.9Hz, quinazolinone H-5), 7.73 (q, 1H, J_{H-F}=4.5Hz, J_{H-H}=4.0Hz, quinazolinone H-7), 7.50-7.48 (m, 1H, quinazolinone H-8), 4.08 (q, 2H, *J*=7.5Hz, CH_2), 1.44 (t, 3H, *J*=7.5Hz, CH_3); ^{13}C-NMR: δ 162.1 (quinazolinone C-4), 160.1 (quinazolinone C-6), 145.6 (quinazolinone C-2), 144.7 (quinazolinone C-9), 129.8 (quinazolinone C-10), 123.4 (quinazolinone C-8), 122.8 (quinazolinone C-7), 111.7 (quinazolinone C-5), 42.3 (CH_2), 14.8 (CH_3); *Anal.* Calc. for $C_{10}H_9FN_2O$ (192.2): C, 62.49; H, 4.72; N, 14.58. Found: C, 62.34; H, 4.62; N, 14.45.

6-Chloro-3-ethylquinazolin-4-one (**3c**). White crystals, yield 74.5%; m.p. 104~106°C; IR: 3099.2, 2980.0, 1666.5, 1626.5, 1604.8, 1469.8 cm^{-1}; ^{1}H-NMR: δ 8.28 (d, 1H, *J*=2.5Hz, quinazolinone H-5), 8.06 (s, 1H, quinazolinone H-2), 7.70-7.65 (m, 2H, quinazolinone H-7,8), 4.07 (q, 2H, *J*=7.5Hz, CH_2), 1.43 (t, 3H, *J*=7.5Hz, CH_3); ^{13}C-NMR: δ 159.9 (quinazolinone C-4), 146.6 (quinazolinone C-2), 146.4 (quinazolinone C-9), 134.6 (quinazolinone C-7), 133.1 (quinazolinone C-6), 129.0 (quinazolinone C-5), 126.0 (quinazolinone C-10), 123.2 (quinazolinone C-8), 42.3 (CH_2), 14.8 (CH_3); *Anal.* Calc. for $C_{10}H_9ClN_2O$ (208.6): C, 57.57; H, 4.35; N, 13.43. Found: C, 57.67; H, 4.25; N, 13.43.

6-Bromo-3-ethylquinazolin-4-one (**3d**). White crystals, yield 77.0%; m.p. 76.5~78.5°C; (lit. [13], neither yield nor any properties given). IR: 3085.3, 2978.1, 1664.6, 1600.9, 1587.9, 1465.9 cm^{-1}; ^{1}H-NMR: δ 8.44 (d, 1H, *J*=2.0Hz, quinazolinone H-5), 8.07 (s, 1H, quinazolinone H-2), 7.81 (dd, 1H, *J*=9.2Hz, 1.7Hz, quinazolinone H-7), 7.57 (d, 1H, *J*=8.6Hz, quinazolinone H-8), 4.07 (q, 2H, *J*=7.5Hz,

CH_2), 1.43 (t, 3H, *J*=7.5Hz, CH_3); ^{13}C-NMR: δ 159.7 (quinazolinone C-4), 146.9 (quinazolinone C-2), 146.6 (quinazolinone C-9), 137.3 (quinazolinone C-7), 133.5 (quinazolinone C-5), 129.2 (quinazolinone C-10), 123.5 (quinazolinone C-8), 120.8 (quinazolinone C-6), 42.3 (CH_2), 14.8 (CH_3); *Anal.* Calc. for $C_{10}H_9BrN_2O$ (253.1): C, 47.46; H, 3.58; N, 11.07. Found: C, 47.33; H, 3.48; N, 11.18.

3-Propylquinazolin-4-one (**3e**). White crystals, yield 83.0%; m.p. 82~83°C; (lit. [8], m.p. 95-96 °C). IR: 3075.3, 2964.6, 1674.2, 1610.6, 1562.3, 1471.7 cm^{-1}; ^{1}H-NMR: δ 8.33 (d, 1H, *J*=8.0Hz, quinazolinone H-5), 8.05 (s, 1H, quinazolinone H-2), 7.78-7.71 (m, 2H, quinazolinone H-6,8), 7.51 (t, 1H, *J*=8.0Hz, quinazolinone H-7), 3.98 (t, 2H, *J*=7.5Hz, NCH_2), 1.87-1.82 (m, 2H, CH_2), 1.01 (t, 3H, *J*=7.5Hz, CH_3); ^{13}C-NMR: δ 161.1 (quinazolinone C-4), 148.0 (quinazolinone C-2), 146.6 (quinazolinone C-9), 134.1 (quinazolinone C-7), 127.4 (quinazolinone C-5), 127.2 (quinazolinone C-6), 126.7 (quinazolinone C-10), 122.1 (quinazolinone C-8), 48.6 (NCH_2), 22.7 (CH_2), 11.1 (CH_3); *Anal.* Calc. for $C_{11}H_{12}N_2O$ (188.2): C, 70.19; H, 6.43; N, 14.88. Found: C, 70.14; H, 6.28; N, 15.03.

6-Fluoro-3-propylquinazolin-4-one (**3f**). White crystals, yield 92.2%; m.p. 96~98°C; IR: 3082.6, 2960.7, 1676.1, 1610.6, 1608.1, 1481.3 cm^{-1}; ^{1}H-NMR: δ 8.01 (s, 1H, quinazolinone H-2), 7.95 (dd, 1H, *J*=8.6Hz, 2.9Hz, quinazolinone H-5), 7.73 (q, 1H, $J_{H\text{-}F}$=4.5Hz, $J_{H\text{-}H}$=4.0Hz, quinazolinone H-7), 7.50-7.46 (m, 1H, quinazolinone H-8), 3.98 (t, 2H, *J*=7.5Hz, NCH_2), 1.86-1.81 (m, 2H, CH_2), 1.01 (t, 3H, *J*=7.5Hz, CH_3); ^{13}C-NMR: δ 162.2 (quinazolinone C-4), 160.4 (quinazolinone C-6), 146.0 (quinazolinone C-2), 144.8 (quinazolinone C-9), 129.9 (quinazolinone C-10), 123.6 (quinazolinone C-8), 122.7 (quinazolinone C-7), 111.8 (quinazolinone C-5), 48.8 (NCH_2), 22.7 (CH_2), 11.2 (CH_3); *Anal.* Calc. for $C_{11}H_{11}FN_2O$ (206.2): C, 64.07; H, 5.38; N, 13.58. Found: C, 64.18; H, 5.40; N, 13.44.

6-Chloro-3-propylquinazolin-4-one (**3g**) [CAS number 501917-08-4, but no references given]. White crystals, yield 83.1%; m.p. 130.0~131.5°C; IR: 3085.2, 2956.9, 1674.2, 1612.5, 1556.6, 1469.7 cm^{-1}; ^{1}H-NMR: δ 8.26 (d, 1H, *J*=2.3Hz, quinazolinone H-5), 8.03 (s, 1H, quinazolinone H-2), 7.68-7.65 (m, 2H, quinazolinone H-7,8), 3.97 (t, 2H, *J*=7.5Hz, NCH_2), 1.86-1.82 (m, 2H, CH_2), 1.01 (t, 3H, *J*=7.5Hz, CH_3); ^{13}C-NMR: δ 160.1 (quinazolinone C-4), 146.9 (quinazolinone C-2), 146.7 (quinazolinone C-9), 134.6 (quinazolinone C-7), 133.1 (quinazolinone C-6), 129.1 (quinazolinone C-5), 126.1 (quinazolinone C-10), 123.3 (quinazolinone C-8), 48.8 (NCH_2), 22.7 (CH_2), 11.2 (CH_3); *Anal.* Calc. for $C_{11}H_{11}ClN_2O$ (222.7): C, 59.33; H, 4.98; N, 12.58. Found: C, 59.43; H, 4.94; N, 12.57.

6-Bromo-3-propylquinazolin-4-one (**3h**). White crystals, yield 87.0%; m.p. 132.5~134.5°C; IR: 3075.2, 2955.0, 1666.5, 1610.6, 1597.1, 1465.9 cm^{-1}; ^{1}H-NMR: δ 8.44 (d, 1H, *J*=2.0Hz, quinazolinone H-5), 8.04 (s, 1H, quinazolinone H-2), 7.82 (dd, 1H, *J*=9.2Hz, 1.7Hz, quinazolinone H-7), 7.57 (d, 1H, *J*=8.6Hz, quinazolinone H-8), 3.97 (t, 2H, *J*=7.5Hz, NCH_2), 1.86-1.81 (m, 2H, CH_2), 1.01 (t, 3H, *J*=7.5Hz, CH_3); ^{13}C-NMR: δ 159.9 (quinazolinone C-4), 146.9 (quinazolinone C-2), 146.7 (quinazolinone C-9), 137.3 (quinazolinone C-7), 129.3 (quinazolinone C-5), 129.2 (quinazolinone C-10), 123.5 (quinazolinone C-8), 120.8 (quinazolinone C-6), 48.7 (NCH_2), 22.6 (CH_2), 11.1 (CH_3); *Anal.* Calc. for $C_{11}H_{11}BrN_2O$ (267.1): C, 49.46; H, 4.15; N, 10.49. Found: C, 49.73; H, 4.24; N, 10.45.

3-Allylquinazolin-4-one (**3i**). White crystals, yield 70.0%; m.p. 63~65°C; (lit. [8] m.p. 65-68 °C). IR: 3061.0, 1676.1, 1610.6, 1562.3, 1473.6 cm^{-1}; ^{1}H-NMR: δ 8.33 (d, 1H, *J*=8.0Hz, quinazolinone H-5),

8.04 (s, 1H, quinazolinone H-2), 7.78-7.71 (m, 2H, quinazolinone H-6,8), 7.52 (t, 1H, *J*=8.0Hz, quinazolinone H-7), 6.03-5.98 (m, 1H, CH=C), 5.32-5.26 (m, 2H, C=CH_2), 4.66 (d, 2H, *J*=6.0Hz, CH_2); ^{13}C-NMR: δ 160.9 (quinazolinone C-4), 148.1 (quinazolinone C-2), 146.3 (quinazolinone C-9), 134.4 (CH=C), 131.9 (quinazolinone C-7), 127.6 (quinazolinone C-5), 127.4 (quinazolinone C-6), 126.9 (quinazolinone C-10), 122.2 (quinazolinone C-8), 119.0 (C=CH_2), 48.4 (CH_2); *Anal.* Calc. for $C_{11}H_{10}N_2O$ (186.2): C, 70.95; H, 5.41; N, 15.04. Found: C, 70.99; H, 5.15; N, 15.02.

3-Allyl-6-fluoroquinazolin-4-one (**3j**). White crystals, yield 72.7%; m.p. 79.0~80.5°C; IR: 3090.5, 1666.5, 1610.6, 1574.0, 1458.2 cm^{-1}; ^{1}H-NMR: δ 7.99 (s, 1H, quinazolinone H-2), 7.94 (dd, 1H, *J*=8.6Hz, 2.9Hz, quinazolinone H-5), 7.73 (q, 1H, J_{H-F}=4.5Hz, J_{H-H}=4.0Hz, quinazolinone H-7), 7.51-7.46 (m, 1H, quinazolinone H-8), 6.03-5.95 (m, 1H, CH=C), 5.34-5.26 (m, 2H, C=CH_2), 4.66 (d, 2H, *J*=5.6Hz, CH_2); ^{13}C-NMR: δ 162.4 (quinazolinone C-4), 159.9 (quinazolinone C-6), 145.4 (quinazolinone C-2), 144.8 (quinazolinone C-9), 131.6(CH=C), 129.9 (quinazolinone C-10), 123.3 (quinazolinone C-8), 122.7 (quinazolinone C-7), 119.1 (C=**C**H_2), 111.6 (quinazolinone C-5), 48.4 (CH_2); *Anal.* Calc. for $C_{11}H_9FN_2O$ (204.2): C, 64.70; H, 4.44; N, 13.72. Found: C, 64.51; H, 4.32; N, 13.64.

3-Allyl-6-chloroquinazolin-4-one (**3k**). White crystals, yield 82.5%; m.p. 113~115°C; IR: 3088.7, 1678.1, 1610.6, 1574.8, 1470.0 cm^{-1}; ^{1}H-NMR: δ 8.28 (d, 1H, *J*=2.5Hz, quinazolinone H-5), 8.03 (s, 1H, quinazolinone H-2), 7.71-7.66 (m, 2H, quinazolinone H-7,8), 6.02-5.96 (m, 1H, CH=C), 5.34-5.26 (m, 2H, C=CH_2), 4.65 (d, 2H, *J*=5.5Hz, CH_2); ^{13}C-NMR: δ 159.8 (quinazolinone C-4), 146.4 (quinazolinone C-2), 146.3 (quinazolinone C-9), 134.8 (**C**H=C), 133.2 (quinazolinone C-7), 131.5 (quinazolinone C-6), 129.1 (quinazolinone C-5), 126.2 (quinazolinone C-10), 123.1 (quinazolinone C-8), 119.2 (C=**C**H_2), 48.5 (CH_2); *Anal.* Calc. for $C_{11}H_9ClN_2O$ (220.7): C, 59.88; H, 4.11; N, 12.70. Found: C, 59.80; H, 4.07; N, 12.64.

3-Allyl-6-bromoquinazolin-4-one (**3l**). [CAS number 459416-38-7, but no references given]. White crystals, yield 70.9%; m.p. 118~120°C; IR: 3068.8, 1670.4, 1610.6, 1577.9, 1464.0 cm^{-1}; ^{1}H-NMR: δ 8.45 (d, 1H, *J*=2.5Hz, quinazolinone H-5), 8.05 (s, 1H, quinazolinone H-2), 7.85 (dd, 1H, *J*=9.2Hz, 1.7Hz, quinazolinone H-7), 7.60 (d, 1H, *J*=8.6Hz, quinazolinone H-8), 6.02-5.96 (m, 1H, CH=C), 5.34-5.27 (m, 2H, C=CH_2), 4.65 (d, 2H, *J*=5.5Hz, CH_2); ^{13}C-NMR: δ 159.6 (quinazolinone C-4), 146.7 (quinazolinone C-2), 146.5 (quinazolinone C-9), 137.5 (quinazolinone C-7), 131.5(**C**H=C), 129.4 (quinazolinone C-5), 129.2 (quinazolinone C-10), 123.4 (quinazolinone C-8), 121.1 (quinazolinone C-6), 119.3 (C=**C**H_2), 48.5 (CH_2); *Anal.* Calc. for $C_{11}H_9BrN_2O$ (265.1): C, 49.84; H, 3.42; N, 10.57. Found: C, 49.84; H, 3.38; N, 10.65.

Bioassays

The antifungal activity of all synthesized compounds **3a-l** was tested against three pathogenic fungi, namely *Fusarium oxysporum*, *Gibberella zeae*, and *Valsa mali*, by the poison plate technique [14]. Compounds **3a-l** were dissolved in acetone (10 mL) before mixing with Potato Dextrose Agar (PDA, 90 mL). The final concentration of compounds **3a-l** in the medium were fixed at 50 *μg*/mL. Three kinds of fungi were incubated in PDA at 25±1 °C for 5 days to get new mycelium for antifungal assay,

then a mycelia disk of approximately 0.45 cm diameter cut from the culture medium was picked up with a sterilized inoculation needle and inoculated in the center of PDA plate. The inoculated plates were incubated at 25±1°C for 5 days. Acetone in sterilized distilled water served as control, while hymexazole was used as positive control For each treatment, three replicates were carried out. The radial growth of the fungal colonies was measured on the sixth day and the data were statistically analyzed. The *in vitro* inhibiting effects of the test compounds on the fungi were calculated by the formula CV = $\frac{A-B}{A}$, where A represents the diameter of fungi growth on untreated PDA, B represents the diameter of fungi on treated PDA, and CV represents the rate of inhibition.

References

1. Tobe, M.; Isobe, Y.; Tomizawa, H.; Nagasaki, T.; Obara, F.; Hayashi, H. Structure-Activity relationships of 6-fluoroquinazolines: Dual-acting compounds with inhibitory activities toward both TNF-*α* production and T cell proliferation. *Bioorg. & Med. Chem.* **2003**, *11*, 609-616.
2. Lamberth, C.; Hillesheim, E.; Bassand, D.; Schaub, F. Synthesis and acaricidal activity of 4-pyrimidinyloxy- and 4-pyrimidinylaminoethylphenyl dioxolanes and oxime ethers. *Pest Manag. Sci.* **2000**, *56*, 94-100.
3. Hung, R. Q.; Li, H.Y.; Ma, J. A.; Qiu, D. W. Synthesis of *O*-(4-Quinazolinyl)oxime Ethers and Their Antiviral Activity. *Chem. J. Chin. Univ.* **1996**, *17*, 571-575.
4. Dandia, A.; Singh, R.; Sarawagi, P. Green chemical multi-component one-pot synthesis of fluorinated 2,3-disubstituted quinazolin-4(3H)-ones under solvent-free conditions and their anti-fungal activity. *J. Fluorine Chem.* **2004**, *125*, 1835-1840.
5. Khan, I. A.; Hassan, G.; Ihsanullah.; Khan, M. A. Efficacy of Post-emergence Herbicides for controlling Weeds in Canola. *Asian J. Plant Sci*. **2003**, *2*, 294-296.
6. Jin, Y.; Li, H.Y.; Lin, L. P.; Tan, J. Z.; Ding, J.; Luo, X. M.; Long, Y. Q. Synthesis and antitumor evaluation of novel 5-substituted-4-hydroxy-8-nitroquinazolines as EGFR signaling-targeted inhibitors. *Bioorg. & Med. Chem.* **2005**, *13*, 5613-5622.
7. Wissner, A.; Berger, D. M.; Boschelli, D. H.; Floyd, M. B. Jr.; Greenberger, L. M.; Gruber, B. C.; Johnson, B. D; Mamuya, N.; Nilakantan, R.;. Reich, M. F.; Shen, R.; Tsou, H. R.; Upeslacis, E.; Wang, Y. F.; Wu, B.; Ye, F.; Zhang, N. 4-Anilino-6,7-dialkoxyquinoline-3-carbonitrile Inhibitors of Epidermal Growth Factor Receptor Kinase and Their Bioisosteric Relationship to the 4-Anilino-6,7-dialkoxy- quinazoline Inhibitors. *J. Med. Chem*. **2000**, *43*, 3244-3256.
8. Maillard, J.; Morin, R. M.; Vincent, M. M. J.; Bernard, M. M. Quinazolone anti-inflammatory composition. *US 3047462***, 1962**; [*Chem. Abstr.*, **1963,** *58*, 1474g].
9. Liu, G.; Song, B. A.; Sang, W. J.; Yang, S.; Jin, L. H.; Ding, X. Synthesis and Bioactivity of *N*-Aryl-4-aminoquinazoline Compounds. *Chin. J. Org. Chem*. **2004**, *24*, 1296-1299.
10. Chao, Q.; Deng, L.; Shih, H.; Leoni, L. M.; Genini, D.; Carson, D.A.; Cottam, H. B. Substituted isoquinolines and quinazolines as potential antiinflammatory agents: Synthesis and biological evaluation of inhibitors of tumor necrosis factor. *J. Med. Chem.* **1999**, *42*, 3860-3873.
11. Liu, Z.-H.; Sun, X.-L.; Zhang, S.-Y. An improved Niementowski reaction. *Chin. J. Org. Chem.* **2001**, *21*, 1161-1163.

12. El-Hiti, G. A. Application of Organolithium in Organic Synthesis: A Convenient Synthesis of More Complex 6-Substituted 3H-Quinazolin-4-ones. *Monatsh. Chem.* **2004**, *135*, 323-331.
13. Aquila, B.; Dakin, L.; Ezhuthachan, J.; Lee, S.; Lyne, P.; Pontz, T.; Zheng, X,-L. Preparation of quinazolinone derivatives as B-Raf inhibitors. *WO 2006024834*, **2006**; [*Chem. Abstr.*, **2006**, *144*. 292772].
14. Song, S. Q.; Zhou, L. G.; Li, D.; Tang, D.; Li, J. Q.; Jiang, W. B. Antifungal activity of five plants from Xinjiang. *Nat. Prod. Res. & Dev.* **2004**, *16*, 157-159.

Sample Availability: Samples of the compounds are available from authors.