



## Synthesis and Antifungal Activities of $N^3$ -Substituted Quinazolin-4-one Catalyzed by 3-Methylimidazole Ionic Liquids

G. LIU\*, C.P. LIU, C.N. JI, L. SUN, X.G. LIU, Q.W. WEN and S.G. XU

School of Chemistry and Materials Science, Ludong University, Yantai 264025, P.R. China

\*Corresponding author: Fax: +86 535 6696281; Tel: +86 535 6673048; E-mail: shdliugang@163.com

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$N^3$ -Substituted quinazolin-4-one was synthesized by alkyl bromide and quinazolin-4-one was synthesized by anthranilic acid and formamide, catalyzing in various 3-methylimidazole ionic liquids and TBAB. The results showed that the yield of  $N^3$ -substituted quinazolin-4-one increased appreciably and the reaction time shorted under ionic liquids and TBAB. Using 1-methyl-3-(2-hydroxy-1-3-acetoxypropyl)imidazolium fluoroborate or 1-propyl-3-methylimidazole fluoroborate as catalyst, the yield of  $N^3$ -benzylquinazolin-4-one reached 85.1 and 82.0 %, increased 27 % more than the yield of traditional conditions. The compounds were evaluated for their *in vitro* antifungal activity against *Fusarium graminearum*, *Fusarium oxysporum* and *Cytospora mandshurica*. Compound **3f** inhibited *Fusarium graminearum* with  $EC_{50}$  28.85  $\mu$ g/mL, *Fusarium oxysporum* with  $EC_{50}$  24.68  $\mu$ g/mL and *Cytospora mandshurica* with  $EC_{50}$  37.67  $\mu$ g/mL.

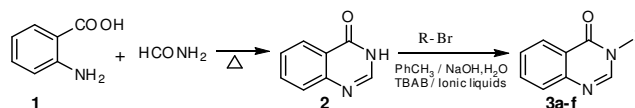
**Key Words:** Quinazolin-4-one, Ionic liquids, Synthesis, Antifungal activity.

### INTRODUCTION

Ionic liquids (IL) provide a useful extension to the range of solvents and catalysts that are available for synthetic chemistry. Some more papers showing an overview of the potential of ionic liquids as solvents for synthesis and catalysis are available<sup>1</sup>. The number of papers and patents being published reflects both academic and industrial interest in using ionic liquids in diverse areas ranging from synthetic and catalytic chemistry to biotechnology, electrochemistry and material science<sup>2</sup>.

Over the past decade, the synthesis of heterocycles has become one of the important aspects of medicinal chemistry<sup>3</sup>. Among the nitrogen-containing heterocycles, substituted quinazolinones represent the medicinally and pharmaceutically important class of compounds because of their wide range of biological activities such as anticancer, diuretic, antiinflammatory, anticonvulsant and antihypertensive activities<sup>4,5</sup>.  $N^3$ -Substituted quinazolin-4-one is a key intermediate for the production of the medicines. However, the yield of  $N^3$ -substituted quinazolin-4-one compounds was low in traditional method. In view of these facts and in order to study the influence of different ionic liquids, we had prepared six  $N^3$ -substituted quinazolin-4-one catalyzing in various 3-methylimidazole ionic liquids. The results showed that every ionic liquid can increase the yield of  $N^3$ -benzylquinazolin-4-one. Using 1-methyl-3-(2-hydroxy-1-3-acetoxy propyl)imidazolium fluoroborate

([HAPmim] BF<sub>4</sub>) or 1-propyl-3-methylimidazole fluoroborate ([Pmim] BF<sub>4</sub>) as catalyst, the yield of  $N^3$ -benzylquinazolin-4-one reached 85.1 and 82.0 % (Scheme-I). To the best of our knowledge, this is the first report on the synthesis of  $N^3$ -substituted quinazolin-4-one catalyzing by [HAPmim]BF<sub>4</sub>. The structures of the title compounds were characterized by IR, <sup>1</sup>H NMR and MS spectroscopy. The preliminary biological tests showed that some of them exhibit good antifungal activities.



Scheme-I: Synthesis route of  $N^3$ -substituted quinazolin-4-one

### EXPERIMENTAL

Unless otherwise indicated, all common reagents and solvents were used as obtained from commercial supplies without further purification. All melting points of the products were determined on a XT-4 binocular microscope (Beijing Tech Instrument Co., China) and are not corrected. The infrared spectra were recorded on a Bruker VECTOR22 spectrometer in KBr disks. <sup>1</sup>H NMR (solvent DMSO-*d*<sub>6</sub>) were recorded on a Bruker AVANCE/AV400 (400 MHz) spectrometer at room temperature using TMS as internal standard. The mass spectra were taken on a GCMS-QP2010 spectrometer. Quinazolin-4-

one (**2**) was prepared according to literature procedure<sup>6</sup>. 3-Methylimidazole ionic liquids were prepared according to literature procedures<sup>7-9</sup>.

### General procedure

**General procedure for preparation of compounds (3a-f):** 1.5g (10 mmol) quinazolin-4-one, (10 mmol) alkyl bromide, 0.26 g (0.8 mmol) TBAB and (0.5 mmol) 3-methylimidazole ionic liquids were added in the mixture of 30 mL toluene and 30 mL 35 % KOH. The mixture was refluxed for 1 h and then cooled to room temperature. The organic layer was separated and washed with distilled water (10 mL × 2). The organic phases were dried (anhyd MgSO<sub>4</sub>), filtered, evaporated under reduced pressure and recrystallized from ethanol to give **3a-f** (Scheme-1).

**N<sup>3</sup>-Benzylquinazolin-4-one (3a):** White crystal; yield 85.1 %, m.p. 116-117 °C. FT-IR (KBr,  $\nu_{\max}$ , cm<sup>-1</sup>): 3035 (Ar-H), 1679.2 (C=O), 1595.7-1456.9 (Ph and quinazoline skeleton vibration), 779.2, 689.2 ( $\delta_{\text{Ph-H}}$ ). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$ : 2.88 (s, 2H, CH<sub>2</sub>), 7.55-8.23 (m, 10H, Ph-H + quinazoline-H). EIMS: *m/z* 236 (M<sup>+</sup>, 16.4).

**N<sup>3</sup>-*n*-Propylquinazolin-4-one (3b):** White crystal; yield 67.7 %, m.p. 93-94 °C. FT-IR (KBr,  $\nu_{\max}$ , cm<sup>-1</sup>): 3035.3 (Ar-H), 2961.9 (CH<sub>3</sub>), 2935.6 (CH<sub>2</sub>), 1664.3 (C=O), 1608.3-1474.0 (quinazoline skeleton vibration). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$ : 1.05 (t, 3H, *J*=7.0 Hz, CH<sub>3</sub>), 1.56-2.16 (m, 2H, CH<sub>2</sub>), 3.96 (t, 2H, *J*=7.2 Hz, NCH<sub>2</sub>), 7.31-7.77 (m, 5H, quinazolinone-H). EIMS: *m/z* 188 (M<sup>+</sup>, 13.5).

**N<sup>3</sup>-*i*-Propylquinazolin-4-one (3c):** White crystal; yield 55.9 %, m.p. 92-93 °C. FT-IR (KBr,  $\nu_{\max}$ , cm<sup>-1</sup>): 3036.4 (Ar-H), 2980.2 (CH<sub>3</sub>), 1664.4 (C=O), 1604.2-1474.8 (quinazoline skeleton vibration), 1383.2, 1365.8 (CH(CH<sub>3</sub>)<sub>2</sub>). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$ : 1.43, 1.55 (2s, 6H, 2CH<sub>3</sub>), 5.10-5.31 (m, 1H, CH), 7.47-8.39 (m, 5H, quinazolinone-H). EIMS: *m/z* 188 (M<sup>+</sup>, 17.2).

**N<sup>3</sup>-(2-Bromoethyl)quinazolin-4-one (3d):** White crystal; yield 48.2 %, m.p. 137-138 °C. FT-IR (KBr,  $\nu_{\max}$ , cm<sup>-1</sup>): 3032.1 (Ar-H), 2976.9 (CH<sub>2</sub>), 1669.9 (C=O), 1608.9-1474.0 (quinazoline skeleton vibration). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$ : 1.62 (t, 2H, *J* = 7.4 Hz, CH<sub>2</sub>), 1.75 (t, 2H, *J* = 7.4 Hz, CH<sub>2</sub>), 7.42-8.14 (m, 5H, quinazolinone-H). EIMS: *m/z* 252 (M<sup>+</sup>, 13.9).

**N<sup>3</sup>-*n*-Butylquinazolin-4-one (3e):** White crystal; yield 52.6 %, m.p. 79-80 °C. FT-IR (KBr,  $\nu_{\max}$ , cm<sup>-1</sup>): 3062.0 (Ar-H), 2955.6 (CH<sub>3</sub>), 2930.6 (CH<sub>2</sub>), 1667.7 (C=O), 1613.2-1472.7 (quinazoline skeleton vibration). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$ : 0.97 (t, 3H, *J* = 7.0 Hz, CH<sub>3</sub>), 1.22-1.92 (m, 4H, CH<sub>2</sub>CH<sub>2</sub>), 4.02 (t, 2H, *J* = 7.2 Hz, NCH<sub>2</sub>), 7.30-8.37 (m, 5H, quinazolinone-H). EIMS: *m/z* 202 (M<sup>+</sup>, 12.1).

**N<sup>3</sup>-Allylquinazolin-4-one (3f):** White crystal; yield 88.2 %, m.p. 64-65 °C. FT-IR (KBr,  $\nu_{\max}$ , cm<sup>-1</sup>): 3078.4 (=CH<sub>2</sub>), 3035.8 (Ar-H), 2926.3 (CH<sub>2</sub>), 1675.2 (C=O), 1615.7 (C=C), 1610.8-1467.2 (quinazoline skeleton vibration). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$ : 4.52-4.58 (m, 2H, CH<sub>2</sub>), 5.12-5.24 (m, 2H, =CH<sub>2</sub>), 5.82-5.95 (m, 1H, =CH), 7.20-8.11 (m, 5H, quinazolinone-H). EIMS: *m/z* 186 (M<sup>+</sup>, 22.7).

**Antifungal assay:** The antifungal activities of **3a-f** were tested against *Fusarium graminearum*, *Fusarium oxysporum* and *Cytospora mandshurica* by mycelia growth inhibition

method<sup>10</sup>. The compounds **3a-f** were dissolved in acetone before mixing with 90 mL potato dextrose agar (PDA). The final concentration of **3a-f** in the medium was 50 µg/mL. All kinds of fungi were incubated in PDA at 27 ± 1 °C for 4 days to get new mycelium for antifungal assay. Then mycelia dishes of *ca.* 4 mm diameter were cut from culture medium and one of them was picked up with a sterilized inoculation needle and inoculated in the center of PDA plate aseptically. The inoculated plates were incubated at 27 ± 1 °C for 5 days. Acetone in sterile distilled water served as control, while hymexazole served as positive control. For each treatment, three replicates were conducted. The radial growth of the 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 represents the diameter of fungi growth on untreated PDA and T represents the diameter of fungi on treated PDA while I means inhibition rate. The EC<sub>50</sub> values were estimated statistically by Probit analysis with Probit package of SPSS 11.5 software using a personal computer<sup>11</sup>. The average EC<sub>50</sub> (µg/mL) was taken (effective dose for 50 % inhibition) from at least three separate analyses for inhibition of growth using the Basic LD<sub>50</sub> program version 1.1. The inhibition effect of **3a-f** in Table-4. The toxicity of **3a-f** in Table-5.

## RESULTS AND DISCUSSION

The reaction results in traditional method or in ionic liquids catalytic method are shown in Table-1. It can be seen that the presence of 3-methylimidazole ionic liquid [HAPmim]BF<sub>4</sub> both accelerated the reactions and gave higher yields. The reaction time for synthesis of compounds **3a-f** was shortened from 2-4 h to 1 h only with added 5 % mol [HAPmim]BF<sub>4</sub>.

TABLE-1  
YIELDS AND REACTION CONDITIONS USED FOR  
IONIC LIQUIDS CATALYTIC SYNTHESIS OF **3a-f**

Product	R	Method A <sup>a</sup>		Method B <sup>b</sup>	
		Reaction time (h)	Yield (%)	Reaction time (h)	Yield (%)
<b>3a</b>	CH <sub>2</sub> Ph	2	57.6	1	85.1
<b>3b</b>	CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	4	38.9	1	67.7
<b>3c</b>	CH(CH <sub>3</sub> ) <sub>2</sub>	4	27.3	1	55.9
<b>3d</b>	CH <sub>2</sub> CH <sub>2</sub> Br	4	16.9	1	48.2
<b>3e</b>	CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	4	24.8	1	52.6
<b>3f</b>	CH <sub>2</sub> CH=CH <sub>2</sub>	4	52.1	1	88.2

Note: a. Reaction conditions of traditional method: **2** (10mmol), alkyl bromide (10 mmol), TBAB (0.8 mmol), 30 mL toluene +30 mL 35 % KOH, reflux 2-4 h; b. Reaction conditions of ionic liquids catalytic method: **2** (10 mmol), alkyl bromide (10 mmol), TBAB (0.8 mmol) and [HAPmim]BF<sub>4</sub> (0.5 mmol), 30 mL toluene +30 mL 35 % KOH, reflux 1 h.

Twelve ionic liquids were used as catalyst to synthesize N<sup>3</sup>-benzylquinazolin-4-one with TBAB. The reaction results with various 3-methylimidazole ionic liquids are shown in Table-2. It can be seen that the presence of 3-methylimidazole ionic liquids both accelerated the reactions and gave higher yields. The reaction time for synthesis of compound **3a** was shortened from 2 h to 1 h with 5 mol % ionic liquids. Using [HAPmim]BF<sub>4</sub> or [Pmim]BF<sub>4</sub> as catalyst, the yield of compound

TABLE-2  
DIFFERENT CONDITIONS USED FOR IONIC LIQUIDS CATALYZED SYNTHESIS OF **3a**

Entry	Ionic liquids	Dosage of ionic liquids (mol %)	Reaction time (h)	Yield (%)
1	[Bmim]Br <sup>a</sup>	5	1	70.1
2	[Bmim]Bph <sub>4</sub> <sup>b</sup>	5	1	65.0
3	[Bmim]BF <sub>4</sub> <sup>c</sup>	5	1	75.1
4	[Bmim]PF <sub>6</sub> <sup>d</sup>	5	1	75.9
5	[Bmim]PF <sub>6</sub> <sup>d</sup>	5	0.25	40.7
6	[Bmim]PF <sub>6</sub> <sup>d</sup>	5	0.5	58.4
7	[Bmim]PF <sub>6</sub> <sup>d</sup>	5	1.5	76.5
8	[Bmim]PF <sub>6</sub> <sup>d</sup>	5	2	76.9
9	[Bmim]PF <sub>6</sub> <sup>d</sup>	2	1	60.9
10	[Bmim]PF <sub>6</sub> <sup>d</sup>	8	1	72.8
11	[Bmim]PF <sub>6</sub> <sup>d</sup>	10	1	68.6
12	[Pmim]BF <sub>4</sub> <sup>e</sup>	5	1	82.0
13	[Pmim]Br <sup>f</sup>	5	1	73.0
14	[Bzmim]Br <sup>g</sup>	5	1	72.8
15	[Bzmim]BF <sub>4</sub> <sup>h</sup>	5	1	71.8
16	[HAPmim]Br <sup>i</sup>	5	1	70.5
17	[HAPmim]NO <sub>3</sub> <sup>j</sup>	5	1	73.9
18	[HAPmim]H <sub>2</sub> PO <sub>4</sub> <sup>k</sup>	5	1	63.9
19	[HAPmim]BF <sub>4</sub> <sup>l</sup>	5	1	85.1
20	NIL <sup>m</sup>	0	2	57.6

Note: Reaction conditions: **2** (10 mmol), benzyl bromide (10 mmol), TBAB (0.8 mmol) and ionic liquids, 30 mL toluene +30 mL 35 % KOH, reflux 1-2 h; TBAB: Tetrabutyl ammonium bromide; a. [Bmim]Br: 1-Butyl-3-methyl imidazolium bromide; b. [Bmim]Bph<sub>4</sub>: 1-Butyl-3-methylimidazolium tetraphenylborate; c. [Bmim]BF<sub>4</sub>: 1-Butyl-3-methylimidazolium tetrafluoroborate; d. [Bmim]PF<sub>6</sub>: 1-Butyl-3-methylimidazolium hexafluorophosphate; e. [Pmim]Br: 1-Propyl-3-methylimidazolium bromide; f. [Pmim]BF<sub>4</sub>: 1-Propyl-3-methylimidazolium tetrafluoroborate; g. [Bzmim]Br: 1-Benzyl-3-methylimidazolium bromide; h. [Bzmim]BF<sub>4</sub>: 1-Benzyl-3-methylimidazolium tetrafluoroborate; i. [HAPmim]Br: 1-Methyl-3-(2-hydroxyl-3-acetoxypropyl) imidazolium Bromide; j. [HAPmim]NO<sub>3</sub>: 1-Methyl-3-(2-hydroxyl-3-acetoxypropyl)imidazolium nitrate; k. [HAPmim]H<sub>2</sub>PO<sub>4</sub>: 1-Methyl-3-(2-hydroxyl-3-acetoxypropyl) imidazolium dihydric phosphate; l. [HAPmim]BF<sub>4</sub>: 1-Methyl-3-(2-hydroxyl-3-acetoxypropyl)imidazolium tetrafluoroborate, m. NIL: no ionic liquids.

**3a** reached 85.1 and 82.0 %, increased *ca.* 27 % more than the yield of traditional conditions (Table-2, entries 12 and 19-20).

In order to optimize the reaction parameters, we selected *N*<sup>3</sup>-benzylquinazolin-4-one catalyzing by [Bmim]PF<sub>6</sub> for further study under different conditions. These results are shown in entries 4-11 of Table-2. Without ionic liquids, *N*<sup>3</sup>-benzylquinazolin-4-one catalyzing by TBAB could be obtained in 57.6 % after 2 h (Table-2, entry 20). When the reaction was carried out under [Bmim]PF<sub>6</sub> and TBAB for 15 min, the yield of *N*<sup>3</sup>-benzylquinazolin-4-one was reduced to 40.7 % and contrasted to 58.7 % when the reaction time was extended to 0.5 h and increased to 75.9 % when the reaction time was extended to 1 h. (Table-2, entries 4-6). However, no further improvement of the yield was noted when the reaction time was prolonged to 1.5 h and 2 h. (Table-2, entries 7-8). Consequently, we chose 1 h as the optimum reaction time (Table-2, entry 4). As for the effect of the dosage of ionic liquids, it could be seen that when it was increased from 2 to 5, 8 and 10 mol %, the yields of *N*<sup>3</sup>-benzylquinazolin-4-one were 60.9, 75.9, 72.8 and 68.6 %, respectively (Table-2, entries 4 and 9-11). Hence, it's better for the reaction to be carried out at 2 mol % or higher dosage settings than only catalyzing by TBAB. No improve-

ment was observed under [Bmim]PF<sub>6</sub> when the dosage of ionic liquids varied from 5-8 and 10 mol % and the yield even decreased a little (Table-2, entries 4 and 10-11), a fact we attribute to the formation of the solubility of ionic liquids.

In order to study catalytic function in different separated 3-methylimidazole ionic liquids, we selected different ionic liquids single handed as catalyst. These results are shown in Table-3. The yield of *N*<sup>3</sup>-benzylquinazolin-4-one was contrasted catalyzing 3-methylimidazole ionic liquids or TBAB.

TABLE-3  
INFLUENCE OF DIFFERENT SEPARATED CATALYST

Entry	Catalyst	Dosage of catalyst (mol %)	Reaction time (h)	Yield (%)
1	[Bmim]Br	5	2	59.7
2	[Bmim]Bph <sub>4</sub>	5	2	50.0
3	[Bmim]BF <sub>4</sub>	5	2	62.7
4	[Bmim]PF <sub>6</sub>	5	2	62.5
5	[Pmim]BF <sub>4</sub>	5	2	58.6
6	[Pmim]Br	5	2	61.7
7	[Bzmim]Br	5	2	62.2
8	[Bzmim]BF <sub>4</sub>	5	2	59.5
9	[HAPmim]Br	5	2	60.8
10	[HAPmim]NO <sub>3</sub>	5	2	63.7
11	[HAPmim]H <sub>2</sub> PO <sub>4</sub>	5	2	57.9
12	[HAPmim]BF <sub>4</sub>	5	2	58.7
13	TBAB	8	2	57.6

Note: Reaction conditions: **2** (10 mmol), benzyl bromide (10 mmol), TBAB (0.8 mmol) or ionic liquids (0.5 mmol), 30 mL toluene +30 mL 35 % KOH, reflux 2 h.

The antifungal activities *in vitro* of these compounds were evaluated against *Fusarium graminearum*, *Fusarium oxysporum* and *Cytospora mandshurica*. The results for title compounds **3a-f** are summarized in Table-4. Toxic regression equation and EC<sub>50</sub> of **3f** inhibited *Fusarium graminearum* with EC<sub>50</sub> 28.85 µg/mL, *Fusarium oxysporum* with EC<sub>50</sub> 24.68 µg/mL and *Cytospora mandshurica* with EC<sub>50</sub> 37.67 µg/mL are summarized in Table-5.

TABLE-4  
INHIBITION RATE OF ANTIFUNGAL ACTIVITY OF **3a-f**

Comp.	Conc. (µg mL <sup>-1</sup> )	Inhibition (%) <sup>a</sup>		
		<i>F. graminearum</i>	<i>F. oxysporum</i>	<i>C. mandshurica</i>
<b>3a</b>	50	21.2	22.1	16.8
<b>3b</b>	50	24.1	22.3	32.5
<b>3c</b>	50	14.6	22.7	13.2
<b>3d</b>	50	29.4	39.4	34.1
<b>3e</b>	50	24.2	12.1	8.1
<b>3f</b>	50	63.6	51.9	60.8
Hymexazole <sup>b</sup>	50	69.5	61.5	65.8

<sup>a</sup>Average of three replicates. <sup>b</sup>Standard drug.

TABLE-5  
TOXIC REGRESSION EQUATION AND EC<sub>50</sub> OF **3f** AGAINST THREE FUNGI

Fungi	EC <sub>50</sub> <sup>a</sup> (µg mL <sup>-1</sup> )	Toxic regression equation <sup>a</sup>	r
<i>F. graminearum</i>	28.85 ± 3.37	y = 2.59x + 2.17	0.996
<i>F. oxysporum</i>	24.68 ± 4.26	y = 2.03x + 3.24	0.988
<i>C. mandshurica</i>	37.67 ± 3.74	y = 2.93x + 2.73	0.994

<sup>a</sup>Average of three replicates.

## Conclusion

In summary, the present new method of *N*<sup>3</sup>-substituted quinazolin-4-one catalyzing in various 3-methylimidazole ionic liquids and TBAB offers several advantages *i.e.*, faster reaction rates and excellent yields. Using [HAPmim]BF<sub>4</sub> or [Pmim]BF<sub>4</sub>, the yield of *N*<sup>3</sup>-benzylquinazolin-4-one reached 85.1 and 82.0 %, increased *ca.* 27 % more than the yield of traditional conditions. Unfortunately, the yield of *N*<sup>3</sup>-benzylquinazolin-4-one was contrasted catalyzing in 3-methylimidazole ionic liquids or TBAB lonely. *N*<sup>3</sup>-Substitued reaction can be promoted catalyzing both of them. The compounds were evaluated for their *in vitro* antifungal activity against *Fusarium graminearum*, *Fusarium oxysporum* and *Cytospora mandshurica*. Compound **3f** inhibited *Fusarium graminearum* with EC<sub>50</sub> 28.85 µg/mL, *Fusarium oxysporum* with EC<sub>50</sub> 24.68 µg/mL and *Cytospora mandshurica* with EC<sub>50</sub> 37.67 µg/mL. Unfortunately, the other tested compounds exhibited a low antifungal activity against *Fusarium graminearum*, *Fusarium oxysporum* and *Cytospora mandshurica*.

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