Bulgarian Chemical Communications, Volume 49, Number 1 (pp. 145 – 150) 2016

Synthesis and anti-plant pathogenic fungal activity of novel benzofuran-2-carboxamide derivatives

Y. Xin*, H. Wang, F. Chen

School of Pharmacy, Chengdu Medical College, Chengdu, 610083, China

Received September 17, 2014; Revised April 28, 2016

Prompted by the various biological activities of carboxamides and benzofurans, a series of substituted benzofuran-2-carboxamide derivatives (**10a-10j** and **11a-11j**) were synthesized and evaluated for anti-plant pathogenic fungal activity. Some of the novel benzofuran-2-carboxamide derivatives exhibited good antifungal activity against four plant pathogenic fungi. Compound **10g** showed good antifungal activity at 200 mg L^{-1} and is hoped to be a potential lead compound.

Keyword: Synthesis, anti-plant pathogenic fungal activity, benzofuran-2-carboxamide.

INTRODUCTION

Agricultural fungal diseases are a cause of major economic loss to agriculture [1,2]. At present, chemical control of fungal diseases is mainly achieved by several classes of chemicals, such as carboxamides, methoxyacrylates, pyrimidinamines, triazoles and so on [3-5]. Among them the carboxamide fungicides have played an important role in the market for fungicides [6,7]. They can inhibit the growth of pathogens and cause their eventual death by interfering with the respiration of the pathogen [8,9]. However, fungicide resistances were observed in fungal populations [10,11].

In order to overcome the threat of widespread multifungicide resistances in plant pathogenic fungi, there is ongoing demand for new fungicide agents.

Literature survey reveals that benzofurans having various amide, ester, ether and thioether derivatives with varying functional groups show antifungal activity [12-15], while little work is reported on benzofuran-2-carboxamide derivatives application in agriculture as fungicides.

Hence, we designed and synthesized (Figure 1) novel benzofuran-2-carboxamide derivatives. They were tested for antifungal activity against *Rhizoctonia solani* (*R. solani*), *Bipolaris maydis* (*B. maydis*), *Gibberella zeae* (*G.zeae*) and *Botrytis cirerea* (*B. cirerea*). To the best of our knowledge, this is the first report on benzofuran-2-carboxamide derivatives with potential controlling effect against plant pathogenic fungi.

EXPERIMENTAL

Material and Equipment

All reagents used were commercial and were used without further purification unless otherwise indicated. Analytical thin-layer chromatography was performed with silica gel plates (60 GF254, Qingdao Haiyang Chemical Co., Ltd., Qingdao, Shandong Province, China). ^{1}H NMR spectra were recorded in deuterochloroform solution on a Bruker 400 MHz spectrometer, using tetramethylsilane (TMS) as an internal standard.

Synthesis of Compounds

1. Synthesis of benzofuran-2-carboxylic acid (4)

*1.1. Synthesis of coumarin dibromide (**2**)*

A solution of Br_2 (100 mmol) in $CHCl_3$ (8.5 mL) was dropwise added to a well stirred solution of compound **1** (100 mmol) and $CHCl_3$ (20 mL) at room temperature for 3 h. Then a solution of Na_2SO_3 (20%, 20 mL) was added till the excess Br_2 was removed. The organic layer was separated, washed and dried. Finally, the solvent was removed in vacuum to give a pale yellow compound **2** in a yield of 86 % [16].

*1.2. Synthesis of benzofuran-2-carboxylic acid (**4**)*

KOH (800 mmol) was dissolved in absolute ethanol (70 mL) and cooled to 15^{o}C. Then compound **2** (70 mmol) was added to the above well stirred solution in 30 min. Finally, the reaction mixture was refluxed for 30 min, and crushed ice was added. Concentrated HCl was added till the pH value of the solution was 1. The crude product was collected, washed, dried and recrystallized to give compound **4** in a yield of 79 % [16].

2. Synthesis of 3-methylbenzofuran-2-carboxylic acid (7).

*2.1. Synthesis of compound (**6**)*

A solution of compound **5** (1.36 g), K_2CO_3 (3 g), KI (1.65 g) and acetone (40 mL) was dropwise added to a well stirred solution of ethyl bromoacetate (20 mmol) at room temperature in 1 h. Then the mixture was refluxed for 2 h. Finally, the solution was cooled

* To whom all correspondence should be sent:
E-mail: tibet99@tom.com

to room temperature and filtered. The liquid was distilled and compound **6** was obtained in a yield of 84 % [17].

2.2. Synthesis of compound (7)

A solution of compound **6** (20 mmol), absolute ethanol (25 mL) and $NaOC_2H_5$ (3.4 g) was refluxed for 15 h. Then ethanol was removed from the reaction mixture, the resulting mixture was added to H_2O and the solution was neutralized. Finally the organic layer was separated, washed and dried. The solvent was removed in vacuum to give compound **7** in a yield of 64 % [17].

3. Synthesis of compounds (**8**) and (**9**)

Thionyl chloride (20 mL) was added to compound **4** or **7** (15 mmol) and the mixture was refluxed for 1 h. Then the excess thionyl chloride was removed in vacuum. The crude product **8** or **9** was obtained and used in the subsequent reaction without further purification [18].

4. General procedure for the preparation of the target compounds **10a-10j** and **11a-11j**.

A mixture of NaOH solution (2 mol L^{-1}, 10 mL) and arylamine (5 mmol) cooled to 0°C was added to compound **8** or **9** (5 mmol) in 10 min. Then the reaction mixture was stirred at room temperature for another 5 h. Finally, the mixture was turned into H_2O and the precipitate was collected by filtration. The pure compounds **10a-10j** and **11a-11j** were obtained by recrystallization in anhydrous ethanol in yields of 30–73%. All compounds are listed in Table 1 and the ^{1}H NMR spectral data are as follows [18]:

N-phenylbenzofuran-2-carboxamide **(10a)**

Pale brown solid, yield: 86.3 %;^{1}H-NMR (400 MHz, $CDCl_3$): 7.17-7.19 (m,1H), 7.32-7.34 (m,1H), 7.38-7.41 (m,2H), 7.45-7.47 (m,1H), 7.56-7.57 (m,1H), 7.60 (s,1H), 7.70-7.73 (m,3H).

N-(2-chlorophenyl)benzofuran-2-carboxamide **(10b)**

White crystals, yield: 74.2 %； ^{1}H-NMR (400 MHz, $CDCl_3$): 7.10-7.13 (m,1H), 7.33-7.36 (m,2H), 7.44-7.49 (m,2H), 7.60-7.63 (m,2H), 7.71-7.73 (m,1H), 8.57-8.58 (m,1H), 8.97 (s,1H).

N-(3-chlorophenyl)benzofuran-2-carboxamide **(10c)**

Pale brown solid, yield: 70.1 %; ^{1}H-NMR (400 MHz, $CDCl_3$): 7.13-7.15 (m,1H), 7.26-7.34 (m,2H), 7.44-7.48 (m,1H), 7.53-7.59 (m,3H), 7.69 (d,1H), 7.84 (s,1H), 8.39 (s,1H).

N-(2-fluorophenyl)benzofuran-2-carboxamide **(10d)**

Pale brown solid, yield: 85.5 %;； H-NMR (400 MHz, $CDCl_3$): 7.11-7.20 (m,`1H), 7.31-7.35 (m,1H), 7.45-7.49 (m,1H), 7.58-7.62 (m,2H), 7.71 (d,1H), 8.48-8.53 (m,1H), 8.61 (s,1H).

N-(4-fluorophenyl)benzofuran-2-carboxamide **(10e)**

Pale brown solid, yield: 81.3 %; H-NMR (400 MHz, $CDCl_3$): 7.11-7.20 (m,`1H), 7.31-7.35 (m,1H), 7.45-7.49 (m,1H), 7.58-7.62 (m,2H), 7.71 (d,1H), 8.48-8.53 (m,1H), 8.61 (s,1H).

N-(naphthalen-1-yl)benzofuran-2-carboxamide **(10f)**

Purple solid, yield: 63.9 %;^{1}H-NMR (400 MHz, $CDCl_3$): 7.25-7.37 (m,2H), 7.42-7.65 (m,5H), 7.72-7.82 (m,2H), 7.90-7.92 (m,1H), 8.01-8.03 (m,1H), 8.17-8.19 (m,1H), 8.83 (s,1H).

N-((furan-2-yl)methyl)benzofuran-2-carboxamide **(10g)**

Pale brown solid, yield: 87.8 %; ^{1}H-NMR (400 MHz, $CDCl_3$): 4.68 (d,2H), 6.33-6.36 (m,2H), 6.96 (s,1H), 7.26-7.31 (m,1H), 7.36-7.43 (m,2H), 7.47-7.55 (m,2H), 7.62-7.66 (m,1H).

N-phenethylbenzofuran-2-carboxamide **(10h)**

Pale yellow solid, yield: 91.5 %;^{1}H-NMR (400 MHz, $CDCl_3$): 2.96 (t,2H), 3.73-3.77 (m,2H), 6.70 (s,1H), 7.25-7.30 (m,4H), 7.33-7.35 (m,2H), 7.39-7.41 (m,1H),7.45-7.46 (m,2H) , 7.66-7.67 (m,1H).

N-(pyridin-3-yl)benzofuran-2-carboxamide **(10i)**

Gray solid, yield: 93.4 %; ^{1}H-NMR (400 MHz, $CDCl_3$): 7.33-7.37 (m,2H), 7.47-7.51 (m,1H), 7.57-7.59 (m,1H), 7.64 (s,1H), 7.72-7.74 (m,1H), 8.33-8.37 (m,1H), 8.42-8.48 (m,2H), 8.79 (s,1H).

N-(2-chloropyridin-3-yl)benzofuran-2-carboxamide **(10j)**

Pale brown crystals, yield: 78.6 %; ^{1}H-NMR (400 MHz, $CDCl_3$): 7.32-7.38 (m,2H), 7.48-7.52 (m,1H), 7.61-7.74 (m,2H), 8.18 (s,1H), 8.89-8.93 (m,2H).

3-methyl-N-phenylbenzofuran-2-carboxamide **(11a)**

Pale brown crystals, yield: 86.5 %; ^{1}H-NMR (400 MHz, $CDCl_3$): 2.69 (s.3H), 7.14-7.18 (m,1H), 7.31-7.35 (m,1H), 7.36-7.41 (m,2H), 7.44-7.53 (m,2H), 7.64-7.66 (m,1H), 7.70-7.73 (m,2H), 8.35 (s,1H).

N-(2-chlorophenyl)-3-methylbenzofuran-2-carboxamide **(11b)**

White crystals, yield: 81.7 %;^{1}H-NMR (400 MHz,$CDCl_3$): 2.70 (s,3H), 7.09-7.11 (m,1H), 7.31-7.36 (m,2H), 7.43-7.50 (m,2H), 7.54-7.56 (m,1H), 7.65-7.67 (m,1H), 8.56-8.59 (m,1H), 8.98 (s,1H).

N-(3-chlorophenyl)-3-methylbenzofuran-2-carboxamide **(11c)**

White solid, yield: 76.2 %;^{1}H-NMR (400 MHz, $CDCl_3$): 2.6 (s,3H), 7.13-7.15 (m,1H), 7.28-7.36 (m,2H), 7.45-7.56 (m,3H), 7.65-7.67 (m,1H), 7.87 (t,1H), 8.35 (s,1H).

N-(2-fluorophenyl)-3-methylbenzofuran-2-carboxamide **(11d)**

Pale brown crystals, yield: 88.6 %; ^{1}H-NMR (400 MHz, $CDCl_3$): 2.69 (s,3H), 7.11-7.21 (m,3H), 7.32-7.36 (m,1H), 7.45-7.49 (m,1H), 7.53-7.55 (m,1H), 7.65-7.67 (m,1H), 8.48-8.53 (m,1H), 8.61 s,1H).

N-(4-fluorophenyl)-3-methylbenzofuran-2-carboxamide **(11e)**

Pale yellow crystals, yield: 81.5 %; ^{1}H-NMR (400 MHz, $CDCl_3$): 2.68(s,3H), 7.06-7.10(m,2H), 7.31-7.35(m,1H), 7.44-7.52(m,2H), 7.64-7.69 (m,2H), 7.65(s,1H).

3-methyl-N-(naphthalen-1-yl)benzofuran-2-carboxamide **(11f)**

White crystals, yield: 92.6 %;^{1}H-NMR (400 MHz, $CDCl_3$): 2.72(s,3H), 7.34-7.37(m,1H), 7.47-7.62(m,5H), 7.68-7.69(m,1H), 7.74-7.76(m,1H), 7.88-7.92(m, 1H), 8.03-8.05(m,1H), 8.18-8.20(m,1H), 8.83(s,1H).

N-((furan-2-yl)methyl)-3-methylbenzofuran-2-carboxamide **(11g)**

Brown crystals, yield: 78.4 %;^{1}H-NMR (400 MHz, $CDCl_3$): 2.64(s,3H), 4.65(d,2H), 6.32-6.36(m,2H), 6.94(s,1H), 7.26-7.30(m,1H), 7.38-7.43(m,3H), 7.59-7.61(m,1H).

3-methyl-N-phenethylbenzofuran-2-carboxamide **(11h)**

Yellow crystals, yield: 87.9 %; ^{1}H-NMR (400 MHz, $CDCl_3$): 2.64 (s,3H), 2.95 (t,2H), 3.25 (q,2H), 6.72 (s,1H), 7.25-7.30 (m,4H), 7.32-7.35 (m,2H), 7.39-7.40 (m,2H), 7.59-7.61 (m,1H).

3-methyl-N-(pyridin-3-yl)benzofuran-2-carboxamide **(11i)**

Yellow solid, yield: 88.0 %; ^{1}H-NMR (400 MHz, $CDCl_3$): 2.69 (s,3H), 7.33-7.37 (m,2H), 7.47-7.54 (m,2H), 7.66-7.68 (m,1H), 8.35-8.40 (m,3H), 8.78 (s,1H).

N-(2-chloropyridin-3-yl)-3-methylbenzofuran-2-carboxamide **(11j)**

White crystals, yield: 82.5 %;^{1}H-NMR (400 MHz, $CDCl_3$): 2.69 (s,3H), 7.31-7.37 (m,2H), 7.48-7.52 (m,1H), 7.56-7.58 (m,1H), 7.66-7.68 (m,1H), 8.15-8.17 (m,1H), 8.91-8.93 (m,1H), 8.95 (s,1H).

In Vitro Antifungal Activity Test

For preliminary evaluation of compounds **10a-10j** and **11a-11j** the antifungal tests of *R. solani*, *B. maydis*, *G.zeae* and *B. cirerea* were carried out using the plate growth rate method [19]. The fungi were obtained from the Institute of Pesticide and Crop Protection, Sichuan University.

The tested compounds were dissolved in acetone and added to a sterile agarized Czapek-Dox medium at 45°C. In primary screenings the compounds were used at a concentration of 200 mg L^{-1}. The control sample contained only one equivalent of acetone. The media were poured onto 8-cm Petri dishes (10 mL for each dish) and after 2 days were inoculated with 4 mm potato dextrose agar (medium) discs of overgrown mycelium. The Petri dishes were incubated at 26 °C in the dark. Two or seven days after inoculation the diameters of the cultures were measured. The percentage of inhibition of fungal growth was determined by comparison between the development of fungi colonized on media containing compounds and on the control. Carbendazim and Boscalid, commercial fungicides, were used as a positive control. Three replicates of each test were carried out and the results were statistically treated.

RESULTS AND DISCUSSION

Chemistry

The synthesis of intermediates and target compounds was performed as illustrated in Scheme 1, Scheme 2, Scheme 3 and Table 1. To synthesize target compounds **10a-10j** and **11a-11j**, the intermediates **4** and **7** were prepared in three steps. First, compound **1** was reacted with Br_2 by addition reaction to produce compound **2**. Then compound **2** was rearranged under KOH to obtain compound **3**. Finally, compound **3** was acidified by HCl to give compound **4**.

Compound **7** was prepared in two steps. First, compound **5** was reacted with ethyl bromoacetate under K_2CO_3 to produce compound **6** which was rearranged under $NaOC_2H_5$ to give compound **7**.

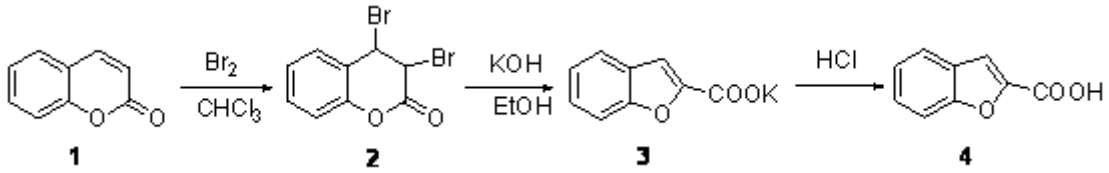
Then compound **4** or **7** was reacted with $SOCl_2$ to obtain compound **8** or **9**. Finally, compound **8** or **9** was reacted with various substituted aromatic amines by amidation to obtain the target compounds **10a-10j** and **11a-11j**.

Antifungal Activity Evaluation

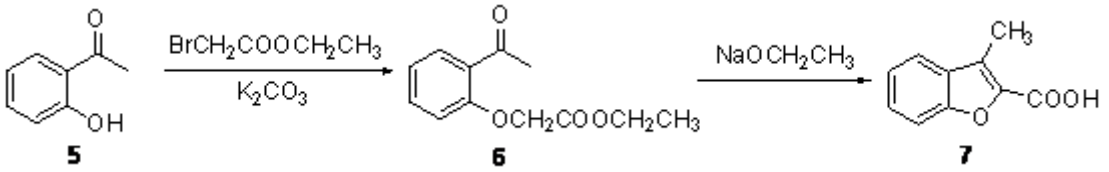
The results of the antifungal activity of compounds **10a-10j** and **11a-11j** against *R. solani*, *B. maydis*, *G. zeae* and *B. cirerea* are listed in Table 2, in which the antifungal activities are expressed as inhibition of growth. We compared the growth rate of fungi on a medium containing a vehicle with the growth rate of fungi on a pure medium. The result indicated that the vehicle for compounds showed no visible antifungal activity.

The results of Table 2 show that the target compounds **10a-10j** and **11a-11j** are active against nearly four fungi at 200 mg L^{-1}. Some of the compounds showed good antifungal activities against *R. solani*. For example, the inhibition of the growth of compounds **10f** and **10g** reached 78.68 % and 65.68 % against *R. solani* at 200 mg L^{-1}, respectively. Compounds **10g** and **10i** exhibited good antifungal activities against *B. maydis*. Their

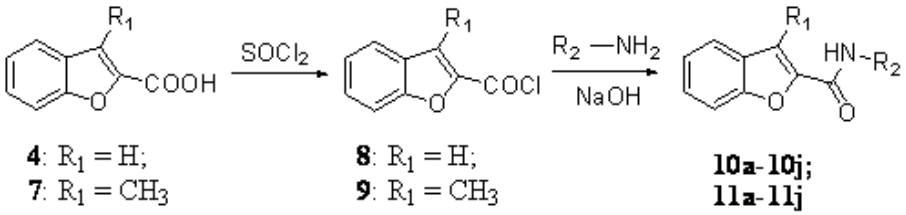
inhibition ratios were 80.57 % and 78.36 %, respectively. Compound **10g** had good inhibition against *B. cirerea* and the inhibition ratio was 68.33 %. Compound **10g** was expected to be a potential lead compound.



Scheme 1. Synthesis of benzofuran-2-carboxylic acid (**4**).



Scheme 2. Synthesis of 3-methylbenzofuran-2-carboxylic acid (**7**).



Scheme 3. Synthesis of target compounds**10a-10j** and**11a-11j**.

Table 1. Structures of benzofuran-2-carboxamide derivatives.

Compound	R_1	R_2	Compound	R_1	R_2
10a	H	phenyl	**11a**	CH_3	phenyl
10b	H	2-chlorophenyl	**11b**	CH_3	2-chlorophenyl
10c	H	3-chlorophenyl	**11c**	CH_3	3-chlorophenyl
10d	H	2-fluorophenyl	**11d**	CH_3	2-fluorophenyl
10e	H	4-fluorophenyl	**11e**	CH_3	4-fluorophenyl
10f	H	1-naphthalenyl	**11f**	CH_3	1-naphthalenyl
10g	H	2-furanylmethyl	**11g**	CH_3	2-furanylmethyl
10h	H	phenethyl	**11h**	CH_3	phenethyl
10i	H	3-pyridinyl	**11i**	CH_3	3-pyridinyl
10j	H	2-chloro-3-pyridinyl	**11j**	CH_3	2-chloro-3-pyridinyl

Table 2. Antifungal activity of benzofuran-2-carboxamide derivatives at 200 mg L^{-1}.

Compound	Inhibition of growth (%)			
	R. solani	*B. maydis*	*G. zeae*	*B. cirerea*
10a	3.15	5.46	3.85	5.68
10b	5.23	14.26	5.39	16.34
10c	4.56	20.25	21.47	10.05
10d	25.79	6.37	2.04	24.18
10e	56.37	14.88	14.06	10.35
10f	78.68	66.41	32.64	49.88
10g	65.68	80.57	28.69	68.33
10h	4.14	39.26	14.05	18.24
10i	57.22	78.36	25.03	66.78
10j	29.29	22.12	11.66	6.28
11a	58.95	32.06	16.08	42.37
11b	18.23	32.11	4.31	11.00
11c	13.34	29.26	3.23	19.21
11d	47.26	7.78	3.69	41.06
11e	38.00	26.56	4.46	53.07
11f	15.17	20.57	34.29	46.41
11g	22.25	20.69	9.37	42.24
11h	63.87	53.35	24.06	49.45
11i	24.96	44.33	14.08	28.26
11j	12.36	12.26	8.20	5.60

CONCLUSIONS

In summary, 20 novel benzofuran-2-carboxamide derivatives **10a-10j** and **11a-11j** were synthesized and evaluated for their antifungal activity against four plant pathogenic fungi (*R. solani*, *B. maydis*, *G. zeae*, *B. cirerea*). The results showed that some of the synthesized compounds exhibited good antifungal activities at 200 mg L^{-1} and compound **10g** is expected to be a potential lead compound. Furthermore, these preliminary results are promising and beneficial for further studies in developing new and more effective fungicides in the agrochemical field. Further structural modification and biological evaluation of these compounds are ongoing in our laboratory.

Acknowledgements: *This work was supported by the Research Program of Department Education of Sichuan Province (11ZB171).*

REFERENCES

1. M. J. Gilbert, C. R. Thornton, E. Gavin, G. E. Wakley, N. J. Talbot, *Nature*, **440**, 535 (2006).
2. L. P. Partida-Martinez, C. Hertweck, *Nature*, **437**, 884 (2005).
3. P. E. Russell, *J. Agric. Sci.*, **143**, 11 (2005).
4. M. T. McGrath, *Plant. Dis.*, **85**, 236 (2001).
5. C. Lamberth, S. Jeanmart, T. Luksch, A. Plant, *Science*, **341**, 742 (2013).
6. J. C. Yang, J. B. Zhang, B. S. Chai, C. L. Liu, *Agrochemicals*, **47**, 6 (2008).
7. W. Krämer, U. Schirmer, P. Jeschke, M, Witschel, 'Modern Crop Protection Compounds', Wiley-VCH Verlag & Co. KGaA, Weinheim, 2012.
8. Q. C. Huang, *World Pestic.*, **26**, 23 (2004).
9. P. Leroux, *Pestic. Sci.*,**47**, 191 (1996).
10. P. Leroux, G. Berthier, *Crop Prot.*, **7**1, 6 (1988).
11. T. Veloukas, A. N. Markoglou, G. S. Karaoglanidis, *Plant Dis.*, **97**, 118 (2013).
12. M. Masubuchi, H. Ebiike, K. Kawasaki, S. Sogabe, K. Morikami, Y. Shiratori, S. Tsujii, T. Fujii, K. Sakata, M. Hayase, H. Shindoh, Y. Aoki, T. Ohtsuka, N. Shimma, *Bioorg. Med. Chem.*, **11**, 4463 (2003).
13. M. Masubuchi, K. Kawasaki, H. Ebiike, Y. Ikeda, S. Tsujii, S. Sogabe, T. Fujii, K. Sakata, Y. Shiratori, Y. Aoki, T. Ohtsuka, N. Shimma, *Bioorg. Med. Chem. Lett.*, **11**, 1833 (2001).
14. H. Ebiike, M. Masubuchi, P. Liu, K. Kawasaki, K. Morikami, S. Sogabe, M. Hayase, T. Fujii, K. Sakata, H. Shindoh, Y. Shiratori, Y. Aoki, T. Ohtsuka, N. Shimma, Bioorg. *Med. Chem. Lett.*, **12**, 607 (2002).
15. K. Kawasaki, M. Masubuchi, K. Morikami, S. Sogabe, T. Aoyama, H. Ebiike, S. Niizuma, M. Hayase, T. Fujii, K. Sakata, H. Shindoh, Y. Shiratori, Y. Aoki, T. Ohtsuka, N. Shimma, *Bioorg. Med. Chem. Lett.*, **13**, 87 (2003).
16. R. C. Fuson, J. Wayne Kneisley, E. W. Kaiser, *Org. Synth.*, **3**, 209 (1955).
17. J. C. Li, T. S. Rush, W. Li, *Bioorg. Med. Chem. Lett.*, **15**, 4961 (2005).
18. A. A. Marei, R. A. Paphael, *J. Chem. Soc.*, 2624 (1958).
19. H. Jin, Y. C. Geng, Z. Y. Yu, K. Tao, T. P. Hou, *Pestic. Biochem. Physiol.*, **93**, 133 (2009).

СИНТЕЗА НА НОВИ БЕНЗОФУРАН-2-КАРБОКСАМИДОВИ ПРОИЗВОДНИ И ТЯХНАТА АКТИВНОСТ СПРЯМО ПАТОГЕННИ ГЪБИЧКИ

Я. Син*, Х. Уанг, Ф. Чен

Фармацевтичен колеж, Медицински колеж в Ченгду, Китай

Постъпила на 17 септември, 2014 г.; коригирана на 28 април, 2016 г.

(Резюме)

Синтезирани са серия заместени бензофуран-2- карбоксамидови производни (**10a-10j** and **11a-11j**) и е оценена тяхната хербицидна и фунгицидна активност. Някои от тях проявяват добра активност срещу четири патегенни растителни фунги. Съединение **10g** показва добра фунгицидна активност при 200 mg L^{-1} и се предполага да бъде потенциално водещо съединение.