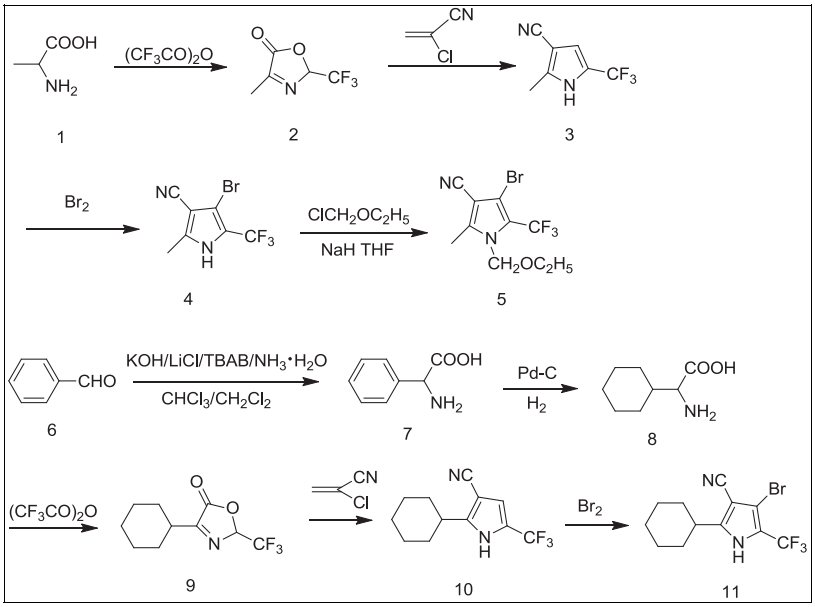
Yongqiang Li, Ziwen Wang, Pengxiang Zhang, Yuxiu Liu,* Lixia Xiong, and Qingmin Wang*

State Key Laboratory of Elemento-Organic Chemistry, Institute of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, People's Republic of China
*E-mail: wang98h@263.net; liuyuxiu@nankai.edu.cn

Received June 12, 2012
DOI 10.1002/jhet.1835
Published online 25 March 2014 in Wiley Online Library (wileyonlinelibrary.com).



To investigate the alkyl analog of insecticide chlorfenapyr, two series of 2-alkyl-4-bromo-5-(trifluoromethyl) pyrrole-3-carbonitriles were synthesized with a cycloaddition as the key step. The target products were characterized by ^{1}H-NMR spectroscopy, elemental analysis, or HRMS. The insecticidal, herbicidal, and antifungal activities of the target compounds were evaluated and found that these compounds did not show much insecticidal activity, but compounds **4**, **10**, and **11** had very good fungicidal activities against *Alternaria solani* and *Fusarium oxysporum*. Moreover, compound **4** had an outstanding inhibition effect against pigweed.

J. Heterocyclic Chem., **51**, 1410 (2014).

INTRODUCTION

4-Bromo-2-(4-chlorophenyl)-1-ethoxymethyl-5-(trifluoromethyl) pyrrole-3-carbonitrile (Fig. 1, **A**), marketed as chlorfenapyr by American Cyanamid [1], was contrived by modifying the structure of the precursor compound **B** (Fig. 1). The study on mechanism of action showed that compound **B** could obstruct the action of oxidation–phosphatization as an uncoupler, whereas chlorfenapyr could not uncouple the oxidation–phosphatization [2], but chlorfenapyr could be activated by the oxidative removal of ethoxymethyl group on 1-position to change into compound **B** and therefore exhibit insecticidal activity *in vivo*[3], so chlorfenapyr actually acted as a proinsecticide of compound **B**. Many modifications towards chlorfenapyr occurred at 1-position; however, none of the analogically structural compounds exhibited superiority over chlorfenapyr. To generate a new lead compound with more superior property, there is a great need to discover some novel pyrrole containing modification at the other positions as precursors of insecticides/miticides [4].

As a continuation of our research on design, synthesis, and bioactive studies of heterocyclic compounds containing pyrrole ring, two series of 2-alkyl-4-bromo-5-(trifluoromethyl) pyrrole-3-carbonitriles were synthesized and evaluated for their insecticidal, herbicidal, and antifungal activities. To the best of our knowledge, the introduction of alkyl group or cycloalkyl group into the 2-position of compound **B** has never been reported because of the synthetic difficulty. Herein, we would like to report the synthesis and bioactivities of the target compounds.

RESULTS AND DISCUSSION

Synthesis. The title compounds **4** and **5** and compounds **10** and **11** were synthesized, respectively, using the depicted routes in Schemes 1 and 2.

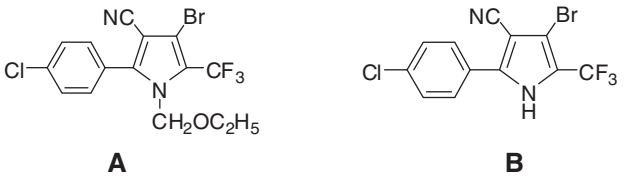
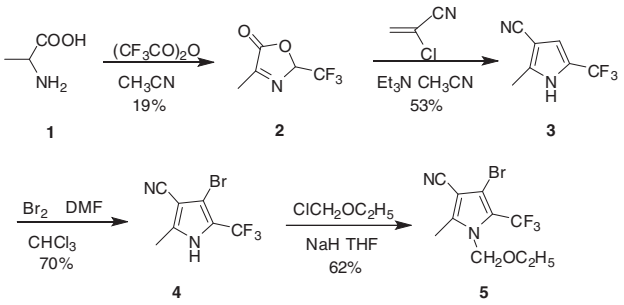


Figure 1. Chemical structures of compounds **A** and **B**.

Scheme 1. Synthetic route of the title compound **4** and **5**.



As shown in Scheme 1, treatment of alanine with trifluoroacetic acid anhydride gave 4-methyl-2-trifluoromethyl-1,3-oxazol-5-one (**2**). Cycloaddition of compound **2** with 2-chloroacrylonitrile in the presence of triethylamine afforded substituted pyrrole (**3**). Bromination of **3** provided the target compound **4**. At last, *N*-alkylation of compound **4** gave the target compound **5** [5].

As the key step, the possible mechanism of cycloaddition reaction according to Tian and coworker's work [6] was depicted in Figure 2. Dehydrogenation of compound **2** gave intermediate **12**. Addition of **12** with 2-chloroacrylonitrile (**13**) afforded **14**, which can cyclize to afford intermediate **16**. Decarboxylation of **16** and further dechlorination reaction gave target product **3**. Intermediate **14** can also obtain a proton to afford byproduct **15**. To decrease the formation of compound **15**, more than two equivalent of ethylamine was added.

The target compounds **10** and **11** (2-cycloalkylpyrrole derivatives) were synthesized (Scheme 2) by using similar synthetic route for the preparation of compounds **4** and **5**. In the procedure, the cyclohexylglycine had to be synthesized using two steps, in which benzaldehyde (**6**) firstly was converted to phenylglycine (**7**), and then reduction of **7** gave intermediate **8** using Pd-C as catalyst.

Biological activities. Unfortunately, none of the target compounds showed insecticidal activity against oriental armyworm, only *N*-ethoxymethyl compound **5** exhibited moderate acaricidal activities against spider mite, larvae of spider mite, and eggs of spider mite (Table 1). However, it was fortunate for us to discover some compounds having good herbicidal and antifungal activities, which was rarely reported in previous articles. For example, the target compound **4** showed good herbicidal activities: 100% inhibition effect against pigweed at the dose of 375 g/ha, over 90% inhibition effect against sowthistle-leaf ixeris and rape at 750 g/ha (Table 2). Table 3 distinctly showed that 2-alkylpyrrole derivatives **4**, **10**, and **11** all displayed very good antifungal activities against *Alternaria solani* and *Fusarium oxysporum*. Compound **4** also exhibited high inhibition against *Cercospora arachidicola*, *Macrophoma kawatsukai*, *Fusahum graminearum in vitro* at the concentration of 50 μg/mL, and *Botrytis cinerea in vivo* at the concentration of 200 μg/mL.

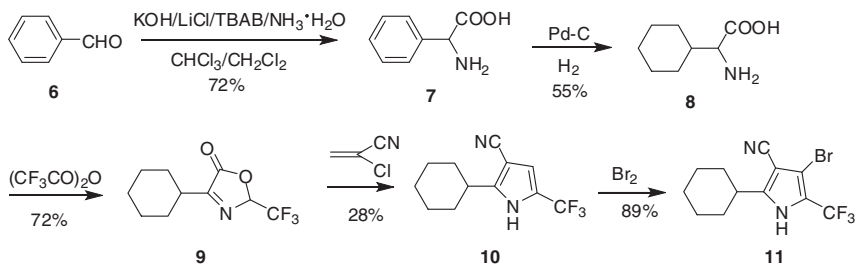
CONCLUSION

In summary, we designed and synthesized two new series of 2-alkyl-4-bromo-5-(trifluoromethyl)pyrrole-3-carbonitriles. The results of bioassay indicated that some compounds had good herbicidal and antifungal activities; for example, compounds **4**, **10**, and **11** had very good fungicidal activities against *A. solani* and *F. oxysporum*. Moreover, compound **4** had an outstanding inhibition effect against pigweed. Therefore, 2-alkylpyrroles might be regarded as precursor compounds for new herbicide and fungicide development.

EXPERIMENTAL

The melting points were determined on an X-4 binocular microscope melting point apparatus manufactured by Beijing Tech Instruments Co., (Beijing, China), and the thermometer was uncorrected. ^{1}H-NMR were obtained using a Bruker AV300 spectrometer (Germany) or a Varian Mercury Plus 400

Scheme 2. Synthetic route of the title compound **10** and **11**.



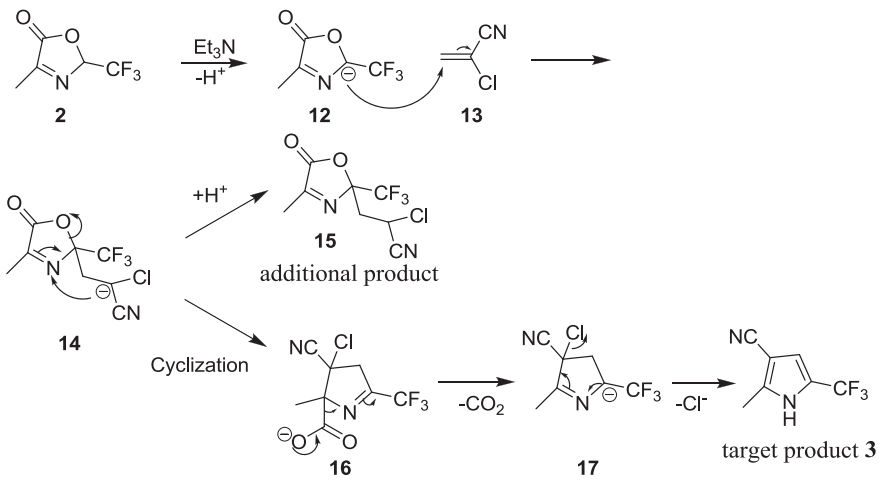


Figure 2. Possible mechanism of **2** to **3**.

Table 1

Insecticidal and acaricidal activities of compounds **4**, **5**, **10**, and **11** against oriental armyworm, spider mite, larvae of spider mite, and eggs of spider mite. [Mortality (%) at different concentration (mg kg^{-1})].

	Oriental armyworm		Spider mite		Larvae of spider mite		Eggs of spider mite	
Compd.	200	100	200	100	200	100	200	100
4	0	—	0	—	0	—	0	—
5	0	—	100	79	100	78	100	85
10	0	—	0	—	0	—	0	—
11	0	—	0	—	0	—	0	—
Chlorfenapyr	100	—	100	100	100	100	100	100

Table 2

Herbicidal activities of compounds **4** [inhibitions (%) at different doses (g/ha), postemergence treatment].

	Rape		Redroot amaranth		Sowthistle-leaf ixeris		Morning glory		Piemarker		Pigweed	
Compd.	750	375	750	375	750	375	750	375	750	375	750	375
4	91.3	64.3	69.1	58.1	92.7	71.6	51.2	14.8	0	—	100	100

Table 3

Antifungal activities of compounds **4**, **10**, and **11** (inhibitions (%), *in vitro*).

	50 μg/mL					200 μg/mL		
Compd.	*Cercospora arachidicol*	*Alternaria solani*	*Macrophoma kawatsukai*	*Fusahum oxysporum*	*Fusahum graminearum*	*Psilocybe cubensis*	*Botrytis cinerea*	*Blumeria graminis*
4	73.6	90.8	100	100	80.6	30	80	0
10	49.6	98.1	36.2	99.3	10.3	60	0	0
11	31.2	98.3	63.4	98.8	30.1	70	0	0

spectrometer (US) in $CDCl_3$ solution with TMS as the internal standard in parts per million (δ). Elemental analyses were determined on a Yanaco CHN Corder MT-3 elemental analyzer (Japan). IR spectra were recorded with an Nicolet MAGNA-560 FTIR spectrometer. HRMS was obtained depending on Ionspec 7.0 T Fourier Transform Ion Cyclotron Resonance Mass Spectrometry (FTICR-MS) (US). All of the reagents were analytically or chemically pure, which were dried and distilled according to standard methods in advance before use.

4-Methyl-2-trifluoromethyl-1,3-oxazol-5-one (2). To a solution of trifluoroactic anhydride (47 g, 0.22 mol) in acetonitrile (100 mL) was added alanine (10 g, 0.11 mol) at 30°C. The mixture was refluxed for 0.5 h and then cooled to RT. The solvent was removed via rotatory evaporator; then, the residue was taken into ethyl acetate (100 mL) and made neutral with saturated Na_2CO_3 solution. The mixture was washed with water (3 × 30 mL) and brine (30 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to obtain a yellow to pale oily liquid, gross yield 19%. ^{1}H-NMR (400 MHz, $CDCl_3$): 6.10–6.07 (m, 1H), 2.40 (s, 3H).

2-Methyl-5-(trifluoromethyl)pyrrole-3-carbonitrile (3). The solution of the compound **2** (3.2 g, 0.019 mol), 2-chloroacrylonitrile (2.5 g, 0.029 mol), and NEt_3 (3.8 g, 0.038 mol) in acetonitrile (40 mL) was refluxed for 2 h and then cooled to RT. The mixture was concentrated *in vacuo*, and the residue was taken into ethyl acetate (100 mL); then, the mixture was washed with water (3 × 30 mL) and brine (30 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The resulting residue was purified by column chromatography on silica gel using petroleum ether/ethyl acetate (3:1, v/v) as the eluent to afford gross product. Finally, the crude product was recrystallized using petroleum ether and ethyl acetate to afford compound **3** (1.7 g) as a slight yellow solid yield 53%, mp 134–135°C. ^{1}H-NMR (400 MHz, $CDCl_3$): 12.85 (s, 1H), 7.00 (s, 1H), 2.34 (s, 3H); *Anal*. Calcd for $C_7H_5N_2F_3$: C, 48.28; H, 2.89; N, 16.09. Found: C, 48.15; H, 3.18; N, 15.72.

2-Methyl-4-bromo-5-(trifluoromethyl)pyrrole-3-carbonitrile (4). To the solution of compound **3** (1.4 g, 0.008 mol) and *N*,*N*-dimethylformamide (0.6 g, 0.008 mol) in chloroform was added dropwise the solution of bromine (1.9 g, 0.012 mol) in chloroform (50 mL). The mixture was refluxed for 1 h and cooled to RT, to which saturated Na_2CO_3 solution (10 mL) was added, and then the mixture was stirred for 30 min. Chloroform and part of the water was removed using rotatory evaporator, and then the remaining mixture was filtered and recrystallized using petroleum ether and ethyl acetate to afford compound **4** (1.4 g) as a white solid, yield 70%, mp 208–210°C. IR: ν 3232, 2233, 1587, 1300, 1174, 711 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): 13.26 (s, 1H), 2.38 (s, 3H); *Anal*. Calcd for $C_7H_4N_2F_3Br$: C, 33.23; H, 1.59; N, 11.07. Found: C, 33.21; H, 1.62; N, 10.93.

2-Methyl-4-bromo-1-ethoxymethyl-5-(trifluoromethyl)pyrrole-3-carbonitrile (5) [7]. To a stirred solution of compound **4** (0.8 g, 0.0031 mol) in THF (20 mL) was added 50% NaH under iced salt bath until no gas was emitted. Then, the mixture was warmed to RT and stirred for 10 min, and then chloromethyl ethyl ether (0.6 g, 0.006 mol) was added dropwise. The mixture was refluxed for 0.5 h, cooled to RT, and then concentrated *in vacuo*. The residue was taken into ethyl acetate (50 mL), washed with water (3 × 30 mL) and brine (30 mL), dried over anhydrous $MgSO_4$, concentrated *in vacuo*, and purified by column chromatography on silica gel using petroleum ether and ethyl acetate (5:1, v/v) as the eluent to afford crude product. Finally, the crude product was recrystallized using petroleum ether and ethyl acetate to afford compound **5** (0.61 g) as a white solid, yield 62%, mp 49–50°C. ^{1}H-NMR (400 MHz, $CDCl_3$): 5.31 (s, 2H), 3.49 (q, $^3J_{HH}$ = 7.2 Hz, 2H), 2.50 (s, 3H), 1.20 (t, $^3J_{HH}$ = 7.2Hz, 3H); *Anal*. Calcd for $C_{10}H_{10}N_2OF_3Br$: C, 38.61; H, 3.24; N, 9.00. Found: C, 38.50; H, 3.28; N, 8.91.

Phenylglycine (7) [8]. To the mixture of KOH (38 g, 0.68 mol), LiCl (9.6 g, 0.23 mol), tetrabutyl ammonium bromide (3.6 g, 0.01 mol), concentrated ammonia (60 mL), and CH_2Cl_2 (30 mL) was blown ammonia gas for 5 min at 0°C, and then a solution of benzaldehyde (12 g, 0.11 mol) and chloroform (20.3 g, 0.17 mol) in methylene dichloride (30 mL) was added dropwise over 1 h. The mixture was stirred and synchronously connected with ammonia gas for 6 h at 0°C. Then, H_2O (60 mL) was added, and the layer was separated. The aqueous layer was washed with CH_2Cl_2 and concentrated *in vacuo* until inorganic salt was precipitated. The solid was filtered off, and the pH value of filtrate was adjusted to 4–6 with dilute hydrochloride to obtain the crystal of compound **7** at 0°C. The crude product was collected by filtration, washed with water, ethanol, and ethyl ether in turn, and dried to give compound **7** (12.3, 72%) as a white solid, which was directly used for the next step without further structural identification.

Cyclohexylglycine (8). The solution of phenylglycine (10 g, 0.066 mol) and 10% Pd-C (2 g) in acetic acid (100 mL) was stirred under hydrogen at 100 atm at 120°C for 72 h, then cooled to RT, and reduced the pressure to 1 atm. The mixture was filtered and concentrated *in vacuo*. The residue was taken into ethanol (100 mL) and refluxed for 30 min, and then propylene oxide was added. The mixture was refluxed for another 10 min, cooled to RT, filtered, washed with ethyl ether, and dried to afford compound **8** (5.7 g, 55%) as a white solid, which was directly used for the next step without further structural identification.

4-Cyclohexyl-2-trifluoromethyl-1,3-oxazol-5-one (9). Compound **9** was synthesized according to the similar synthetic procedure for compound **2**. Yellow oily liquid, yield 72%. ^{1}H-NMR (400 MHz, $CDCl_3$): 6.08 (s, 1H), 2.78 (t, $^3J_{HH}$ = 11.2 Hz, 1H), 2.08–2.00 (m, 2H), 1.88–1.83 (m, 2H), 1.76–1.73 (d, $^3J_{HH}$ = 11.2 Hz, 1H), 1.53–1.23 (m, 5H); HRMS Calcd for $C_{10}H_{12}NO_2F_3$: 258.0712. Found: 258.0713.

2-Cyclohexyl-5-(trifluoromethyl)pyrrole-3-carbonitrile (10). Compound **10** was synthesized according to the similar synthetic procedure for compound **3**. White solid, yield 28%, mp 158–159°C. ^{1}H-NMR (400 MHz, $CDCl_3$): 12.69 (s, 1H), 7.01 (s, 1H), 2.79–2.71 (m, 1H), 1.82–1.16 (m, 4H), 1.68 (d, $^3J_{HH}$ = 12.4 Hz, 1H), 1.64–1.53 (m, 2H), 1.36–1.27 (m, 2H), 1.27–1.17 (m, 1H); *Anal*. Calcd for $C_{12}H_{14}N_2F_3$: C, 59.50; H, 5.41; N, 11.56. Found: C, 59.32; H, 5.59; N, 11.66.

2-Cyclohexyl-4-bromo-5-(trifluoromethyl)pyrrole-3-carbonitrile (11). Compound **11** was synthesized according to the similar synthetic procedure for compound **4**. White solid, yield 89%, mp 203–206°C. ^{1}H-NMR (400 MHz, $CDCl_3$): 13.06 (s, 1H), 2.75 (t, $^3J_{HH}$ = 12 Hz, 1H), 1.82–1.76 (m, 4H), 1.69–1.53 (m, 3H), 1.35–1.16 (m, 3H); *Anal*. Calcd for $C_{12}H_{13}N_2F_3Br$: C, 44.88; H, 3.77; N, 8.72. Found: C, 44.51; H, 4.08; N, 8.65.

Biological tests. The insecticidal activity against oriental armyworm, the acaricidal activity against spider mite, eggs of spider mite, and larvae of spider mite were tested using reported methods in previous literatures [9]. Likewise, the herbicidal and antifungal activities were also tested using the previously reported methods [10]. The insecticidal and acaricidal experiments

including control and chlorfenapyr for comparative purpose were rigorously carried out in three replicate under the same conditions. Assessments were made on a dead/alive basis, and mortality rates were estimated using Abbott's formula [11]. Evaluations are based on a percentage scale of 0–100, which 0 equals no activity and 100 equals total kill or inhibition. The results of insecticidal, acaricidal, herbicidal, and fungicidal activities were listed in Tables 1–3, respectively.

Acknowledgments. This work was supported by the National Key Project for Basic Research (2010CB126100) and the National Natural Science Foundation of China (21072109) and the National Key Technology Research and Development Program (2012BAK25B03-3). We also thank China Agricultural University to supply some of chemical reagents.

REFERENCES AND NOTES

[1] (a) Lovell, J. B.; Wright, D. P.; Gard, I. E.; Miller, T. P.; Treacy, M. F. Proc Brighton Crop Prot Conf 1990, 43; (b) Brown, D. G.; Siddens, J. K.; Diehl, R. E.; Wright, D. P. U.S. patent 5010098, 1988; (c) Nakamura, H.; Shiomi, K.; Iinuma, H.; Naganawa, H.; Obata, T.; Takeuchi, T. J Antibiot 1987, 40, 899.

[2] (a) Kuhn, D. G. ACS Symp 1997, 658, 195; (b) Addor, R. W.; Babcock, T. J.; Black, B. C.; Brown, D. G.; Diehl, R. E.; Furch, J. A.; Kameswaran, V.; Kamhi, V. M. ACS Symp Ser 504 1992, 283.

[3] Hugener, M.; Heimgartner, H. Helv Chim Acta 1989, 72, 172.

[4] (a) Herron, G. A.; Rophail, J.; Wilson, L. J. Exp Appl Acarol 2004, 34, 315; (b) Kameswaran, V. U.S. patent 5130328, 1991; (c) Sperry, J.; Wright, D. Curr Opin Drug Discov Dev 2005, 8, 723.

[5] (a) Hugener, M.; Heimgartner, H. Helv Chim Acta 1989, 72, 172; (b) David, G. K.; Victor, M. K.; Joseph, A. F. Pestic Sci 1994, 41, 279.

[6] (a) Tian, W. S.; Luo, Y. R.; Zai, Y. Q.; Zhai, H. Y. Acta Chem Sinica 1994, 52, 1126; (b) Tian, W. S.; Luo, Y. R.; Chen, Y. J Chem Soc Chem Comm 1993, 2, 101.

[7] Delaude, L.; Laszlo, P. J Org Chem 1990, 55, 5260.

[8] Landini, D.; Montanari, F.; Rolla, F. Synthesis 1979, 26.

[9] (a) Zhao, Q. Q.; Shang, J.; Liu, Y. X.; Wang, K. Y.; Bi, F. C.; Huang, R. Q.; Wang, Q. M. J Agric Food Chem 2007, 55, 9614; (b) Chen, L.; Huang, Z. Q.; Wang, Q. M.; Shang, J.; Huang, R. Q.; Bi, F. C. J Agric Food Chem 2007, 55, 2659; (c) Kuhn, D. G.; Donovan, S. F.; Furch, J. A. U.S. patent 5286743, 1992; (d) Kuhn, D. G.; Kameswaran, V. U.S. patent 5302383, 1993; (e) Zhao, Y.; Mao, C. H.; Li, Y. Q.; Zhang, P. X.; Huang, Z. Q.; Bi, F. C.; Huang, R. Q.; Wang, Q. M. J Agric Food Chem 2008, 56, 7326; (f) Liu, Z. H.; Lei, Q.; Li, Y. Q.; Xiong, L. X.; Song, H. B.; Wang, Q. M. J Agric Food Chem 2011, 59, 12543.

[10] (a) Mo, W. Y.; Yao, Y. Y.; Shen, Y. L.; He, H. W.; Gu, Y. C. J Heterocycl Chem 2009, 46, 579; (b) Yan, M.; Luo, Z. G.; Zhu, X. F.; Shi, D. Q. J Heterocycl Chem 2008, 45, 1045; (c) Wang, H. Q.; Liu, Z. J.; Yang, L. M.; Ding, M. W. J Heterocycl Chem 2004, 41, 393; (d) Yan, X. J.; Liang, X. M.; Jin, S. H.; Lv, J. P.; Yu, C. X.; Qi, W. Y.; Li, B. J.; Yuan, H. Z.; Qi, S. H.; Shi, Y. X.; Wu, J. P.; Chen, F. H.; Wang, D. Q. J Agric Food Chem 2010, 58, 2726; (e) Zhao, Q. Q.; Liu, S. H.; Li, Y. H.; Wang, Q. M. J Agric Food Chem. 2009, 57, 2849.

[11] (a) Song, B. A.; Yang, S.; Hong, Y. P.; Zhang, G. P.; Jin, L. H.; Hu, D. Y. J Fluorine Chem 2005, 126, 1419; (b) Liu, Y. X.; Wei, D. G.; Zhu, Y. R.; Liu, S. H.; Zhang, Y. L.; Zhao, Q. Q.; Cai, B. L.; Li, Y. H.; Song, H. B.; Liu, Y.; Wang, Y.; Huang, R. Q.; Wang, Q. M. J Agric Food Chem 2008, 56, 204; (c) Karegoudar, P.; Prasad, D. J.; Ashok, M.; Mahalinga, M.; Poojary, B.; Holla, B. S. Eur J Med Chem 2008, 43, 808; (d) Jiang, L. L.; Tan, Y.; Zhu, X. L.; Wang, Z. F.; Zuo, Y.; Chen, Q.; Xi, Z.; Yang, G. F. J Agric Food Chem 2010, 58, 2643.