Journal of Fluorine Chemistry 156 (2013) 120–123

Contents lists available at ScienceDirect

Journal of Fluorine Chemistry

journal homepage: www.elsevier.com/locate/fluor

Synthesis and insecticidal activity of novel dihalopropene derivatives containing benzoxazole moiety: A structure–activity relationship study

Aiying Guan, Yukun Qin, Junfeng Wang, Bin Li *

State Key Laboratory of the Discovery and Development of Novel Pesticide, Shenyang Research Institute of Chemical Industry Co. Ltd., Shenyang 110021, China

ARTICLE INFO

Article history:
Received 26 June 2013
Received in revised form 30 August 2013
Accepted 2 September 2013
Available online 12 September 2013

Keywords:
Dihalopropene derivative
Benzoxazole
Active substructure combination
Insecticides

ABSTRACT

Ten dichloropropene derivatives containing benzoxazole moiety were synthesized and bioassayed in order to determine their *in vivo* insecticidal activity. The structures of obtained compounds were identified by ^{1}H NMR, MS and elemental analyses. The bioassay results indicated that compound 2-(3-(2,6-dichloro-4-(3,3-dichloroallyloxy)phenoxy)propoxy)-5-(trifluoromethyl)benzo[*d*]oxazole (5i, R^1 is trifluoromethyl, R^2 is H and *n* is 3) had the optimal structure with best insecticidal activity against *Spodoptera exigua* (100%) at 1 mg/L concentration, highlighting the importance of trifluoromethyl group. The structure–activity relationship of the synthesized compounds was discussed as well.

1. Introduction

Pyridalyl (Fig. 1), a novel dihalopropene insecticide was discovered and developed by Sumitomo Chemical Co., Ltd. and commercialized in 2004. It exhibits excellent insecticidal activities against various lepidopterous and thysanopterous pests on cotton and vegetables, low toxicity to non-target pests and safety to mammals [1,2]. Interestingly, it has been shown that pyridalyl is highly efficient to a strain of *P. xylostella*, which has already developed resistance to synthetic pyrethroids, organophosphates and benzoylureas, probably due to the novel mode of actions of pyridalyl [3–6]. As we know, currently, insect resistance to existing pesticides has become a severe issue in the agrochemical field. Therefore, the development of novel insecticides to fight against this kind of resistance is becoming an intensive research topic. The substructure of 3,3-dichloroallyloxybenzene of pyridalyl has been recognized as pharmacophore in this series of insecticides.

Furthermore, benzoxazole derivatives with particular biological activities are applied widely in the fields of agrochemicals and pharmaceuticals [7], including herbicide metamifop (Fig. 1) [8]. Therefore, using strategies of active substructure combination [9] and bioisosteric replacement [10] via organic synthesis route (Scheme 1), we designed to replace original pyridine ring of pyridalyl with benzoxazole ring using pyridalyl as the lead compound. These two substructures were linked by different length of methylene via oxygen atom. A successful example incorporating benzoxazole with 3, 3-dichloroallyloxybenzene, compound A (Fig. 1, discovered by FMC), had obtained with 100% control against *Heliothis virescens* at 10 ppm [11]. In addition, it is well known that many fluorine-containing compounds exhibit significant agricultural bioactivities owing to fluorine atom's unique properties, such as high thermal stability and lipophilicity [12]. The trifluoromethyl (CF_3) group considered a 'pseudo-halogen', has often been found to impart unique biological activity [13]. Therefore, in this study, a series of new dihalopropene analogs with the substituents of H, Cl and CF_3 was designed with increasing order of electron withdrawing. These compounds were synthesized and their structures were characterized by ^{1}H NMR, MS and elemental analyses. Their insecticidal screening was performed and the excellent insecticidal activity against *Spodoptera exigua* at 1 mg/L of the compound **5i** was discovered. The detailed synthesis, insecticidal activities and structure–activity relationship of this series of compounds were further discussed.

2. Results and discussion

2.1. Synthesis

Starting from substituted 2-aminophenol (**1**), the (un)substituted 2-mercaptobenzoxazole was synthesized by cyclization with carbon disulfide in the presence of potassium hydroxide (step a), followed by chlorination reaction (step b) to afford the key

* Corresponding author. Tel.: +86 2485869128; fax: +86 2485869337.
E-mail address: libin1@sinochem.com (B. Li).

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http://dx.doi.org/10.1016/j.jfluchem.2013.09.003

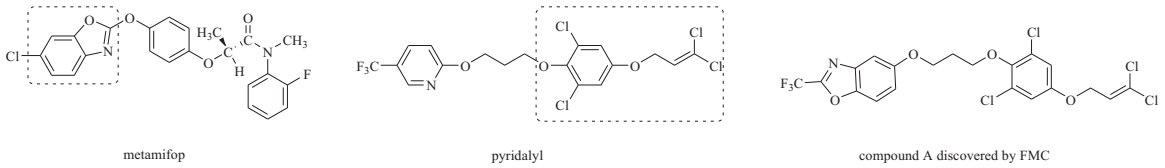
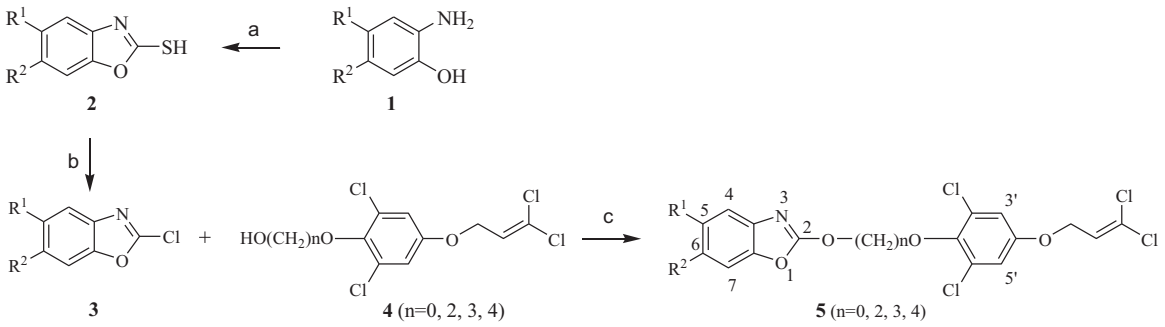


Fig. 1. Chemical structures of metamifop, pyridalyl and compound A.



Scheme 1. Reagents and conditions: (a) potassium hydroxide, CS_2, EtOH/H_2O; (b) $SOCl_2$, DMF, toluene; (c) NaH/THF, room temperature.

intermediate (un)substituted 2-chlorobenzoxazole (**3**). The title compounds (**5**) were prepared in 27–61% yield by reacting compounds (**3**) with 3,3-dichloroallyloxyphenoxy intermediates (**4**) [14] using sodium hydride as a base in tetrahydrofuran at room temperature for 5 h (step c). The synthetic route is illustrated in Scheme 1. The synthesized compounds are listed in Table 1, and their structures were confirmed by ^{1}H NMR, MS and elemental analyses.

2.2. Insecticidal activities

The insecticidal activities *in vivo* were evaluated using a previously reported procedure [15]. The results of compounds **5a**–**5j** against *Spodoptera exigua* were also listed in Table 1. The levels of insecticidal activities were reported in the range 0 (indicates no mortality) to 100% (complete mortality).

As shown in Table 1, all of the synthesized compounds exhibited insecticidal activities against *S. exigua* at 10 mg/L. Compounds **5a**, **5b**, **5e**, **5f**, **5i** and **5j** exhibited 100% control at 10 mg/L while compounds **5e**, **5i** and **5j** displayed better insecticidal activity against *S. exigua*. In particular, compound **5i** showed excellent insecticidal activity with 100% control at 1 mg/L, much higher than that of pyridalyl (50% control at 1 mg/L).

There is a very interesting relationship of structure and activities among these compounds. First of all, linker length of methylene significantly contributes to the insecticidal activity. Generally, compounds (**5a**, **5b**, **5e**, **5i**) with methylene linker of 3 carbon atoms exhibit higher insecticidal activities than compounds with other linker lengths. Therefore, 3-carbon chain is the optimal linker for enhancing the insecticidal activity. Secondly, the electronic effect of R^1 and R^2 of benzoxazole ring plays an important role on insecticidal activity. It is well known that trifluoromethyl is a very strong electron withdrawing group. When R^1 is CF_3 (**5i**), the insecticidal activity against *S. exigua* increased greatly, compared with **5a** in which R^1 is hydrogen (100% versus 25% at 1 mg/L). Alterations of substituents at R^2 exhibit the same trend as R^1 (**5a** versus **5b** versus **5e**). That is, when R^2 is chlorine, a moderate electron withdrawing group (**5b**), its activity is increased compared to **5a** (50% versus 25% at 1 mg/L). Again, when R^2 is trifluoromethyl (**5e**), a stronger electron withdrawing group than chlorine, its activity was further increased to reach 88% at 1 mg/L, indicating a clear picture of the effect of substituents on bioactivity: the stronger of electron withdrawing effect, the higher of bioactivity. Finally, the position of substituent on benzoxazole ring plays a critical role on the insecticidal activity as well. We see higher insecticidal activity in compounds **5j**, **5i** and **5h** with trifluoromethyl group at 5-position as compared to compounds **5f**, **5e** and **5d** with trifluoromethyl group at 6-position. Compound **5i** with 5-position of CF_3 at benzoxazole ring exhibited 100% control at 1 mg/L against *S. exigua*, better than compound **5e** (88%)

Table 1
Chemical structures, physical properties of compounds synthesized and their insecticidal activity against *Spodoptera exigua* (% control, mg/L).

Compd.	R^1	R^2	n	Appearance	mp (°C)	Yield (%)	Insecticidal activity against *Spodoptera exigua* (% control at given concentration mg/L)	
							10	1
5a	H	H	3	Yellow oil	–[a]	47	100	25
5b	H	Cl	3	White s.	58–60	61	100	50
5c	H	CF_3	0[b]	White s.	79–81	61	38	13
5d	H	CF_3	2	Yellow oil	–	51	50	13
5e	H	CF_3	3	Yellow oil	–	52	100	88
5f	H	CF_3	4	Yellow oil	–	27	100	25
5g	CF_3	H	0	White s.	63–65	36	25	0
5h	CF_3	H	2	Yellow oil	–	29	88	13
5i	CF_3	H	3	White s.	46–47	35	100	100
5j	CF_3	H	4	White s.	49–50	29	100	88
Pyridalyl	–	–	–	–	–	–	100	50

[a] No data.
[b] Linker is one oxygen atom.

at 1 mg/L which CF_3 is located at 6-position of benzoxazole ring. Moreover, compound **5j** with 5-position of trifluoromethyl group showed higher insecticidal activity (88% control at 1 mg/L) than compound **5f** with 6-position of trifluoromethyl group (25% control at 1 mg/L) when the linker has four repeated methylene chain. Thus, we conclude that the compound with 5-positon strong electron withdrawing group and 3 carbon linker has the best insecticidal activity in this series of compounds. This SAR indicates that electronic effect (electron withdrawing group) and spatial effect (position of substituent at benzoxazole ring and linker length of methylene group) work together to contribute the bioactivity.

3. Conclusions

The present work demonstrates that dihalopropene derivatives containing benzoxazole moiety with the presence of 5-trifluomethyl group in benzoxazole ring can be used as lead compounds for developing novel insecticides. 5-Trifluomethyl group plays an important role in enhancing the biological activity of target compounds. Further synthesis and structure optimization studies are in progress.

4. Experimental

All starting materials and reagents were commercially available and used without further purification otherwise stated. Melting points were determined on a Büchi melting point apparatus and were uncorrected. ^{1}H NMR spectra were recorded with a Mercury 300 (Varian, 300 MHz) spectrometer with deuterochloroform as the solvent and tetramethylsilane (TMS) as the internal standard. Mass spectra were recorded using a JEOL JMS-700 mass spectrometer. Elemental analyses were determined on a Yanaco MT-3CHN elemental analyzer. All materials for bioassays including insects and 3,3-dichloroallyloxyphenoxy intermediates were obtained from the Agrochemical Discovery Department of the Shenyang Research Institute of the Chemical Industry.

The preliminary insecticidal tests were performed as follows: according to the solubility of testing compounds, the compounds were dissolved in either acetone or dimethyl sulfoxide, and then diluted with 0.1% aqueous solution of Tween 80 to form 50 mL testing solution (the content of acetone or dimethyl sulfoxide in the total solution was not more than 10%). The cabbage leaves were made into plates of 1 cm diameter by punch. A testing solution (0.5 mL) was sprayed by airbrush to both sides of every plate. 8 Third instar larvae were put into the petri-dishes after the leaf disk air-dried and 3 replicates were set for each treatment. Then the insects were maintained in observation room (24 °C, 60–70% R.H.). The number of surviving insects was investigated and mortality was calculated after 96 h.

4.1. General procedure

Potassium hydroxide (46 mmol), ethanol (25 mL) and water (10 mL) were added to a dried round-bottomed flask sequentially, followed by the dropwise addition of CS_2 (25 mmol), after 15 min, (un)substituted 2-aminophenol (23 mmol) was added, then the resulting solution was heated to reflux for 4 h. The reaction solution was acidified to pH~4 with dilute hydrochloric acid and then poured into water, extracted with ethyl acetate, the organic phase was washed with brine, dried over anhydrous magnesium sulfate, concentrated under reduced pressure and the residue was purified via silica gel column chromatography to obtain the intermediate the (un)substituted 2-mercaptobenzoxazole as a yellow solid. Then, the (un)substituted 2-mercaptobenzoxazole (5.5 mmol) was refluxed in $SOCl_2$ (15 mL) for 2 h, excessive $SOCl_2$ was removed under reduced pressure to give (un)substituted 2-chlorobenzoxazole as a yellow solid which was used in next reaction without further purification. Finally, 60% of NaH (1.0 mmol) was added into a solution of 3,3-dichloroallyloxyphenoxy intermediates (1.0 mmol) in THF (5 mL), after 2 h, (un)substituted 2-chloro-benzoxazole (1.0 mmol) was added, the reaction mixture was stirred for another 5 h at room temperature. The reaction mixture was poured into water and extracted with ethyl acetate, the organic phase was washed with saturated sodium bicarbonate, brine, dried over anhydrous magnesium sulfate, concentrated and the residue was purified via silica gel column chromatography to afford the title compounds.

4.1.1. Syntheses of 2-(3-(2,6-dichloro-4-(3,3-dichloroallyloxy)phenoxy)propoxy)benzo[d]oxazole (**5a**)

Yield 47%, oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.49–7.52 (m, 1H, 6-*H*), 7.34–7.37 (m, 1H, 5-*H*), 6.83–7.25 (m, 2H, 4, 7-2*H*), 6.83 (s, 2H, 3′,5′-2*H*), 6.10 (t, 1H, J = 6.3 Hz, CH_2CH), 4.87 (t, 2H, J = 6.0 Hz, $CH_2CH_2CH_2$), 4.57 (d, 2H, J = 6.3 Hz, $CHCH_2$), 4.15 (t, 2H, J = 6.0 Hz, $CH_2CH_2CH_2$), 2.34–2.42 (m, 2H, $CH_2CH_2CH_2$). Anal. Calcd. for $C_{19}H_{15}Cl_4NO_4$: C, 49.27; H, 3.26; N, 3.02. Found: C, 49.37; H, 3.28; N, 2.95.

4.1.2. Syntheses of 6-chloro-2-(3-(2,6-dichloro-4-(3,3-dichloroallyloxy)phenoxy)propoxy)benzo[d]oxazole (**5b**)

Yield 61%, mp: 58–60 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36–7.41 (m, 2H, 5,7-2*H*), 7.21–7.25 (m, 1H, 4-*H*), 6.84 (s, 2H, 3′,5′-2*H*), 6.11 (t, 1H, J = 6.3 Hz, CH_2CH), 4.87 (t, 2H, J = 6.3 Hz, $CH_2CH_2CH_2$), 4.59 (d, 2H, J = 6.3 Hz, $CHCH_2$), 4.15 (t, 2H, J = 5.7 Hz, $CH_2CH_2CH_2$), 2.34–2.41 (m, 2H, $CH_2CH_2CH_2$). Anal. Calcd. for $C_{19}H_{14}Cl_5NO_4$: C, 45.86; H, 2.84; N, 2.81. Found: C, 45.73; H, 3.91; N, 2.86.

4.1.3. Syntheses of 2-(2,6-dichloro-4-(3,3-dichloroallyloxy)phenoxy)-6-(trifluoromethyl)benzo[d]oxazole (**5c**)

Yield 61%, mp: 79–81 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.75 (s, 1H, 4-*H*), 7.58 (s, 2H, 5,7-2*H*), 6.99 (s, 2H, 3′,5′-2*H*), 6.15 (t, 1H, J = 6.3 Hz, CH_2CH), 4.66 (d, 2H, J = 6.3 Hz, $CHCH_2$). Anal. Calcd. for $C_{17}H_8Cl_4F_3NO_3$: C, 43.16; H, 1.70; N, 2.96. Found: C, 43.24; H, 1.76; N, 2.85.

4.1.4. Syntheses of 2-(2-(2,6-dichloro-4-(3,3-dichloroallyloxy)phenoxy)ethoxy)-6-(trifluoromethyl)benzo[d]oxazole (**5d**)

Yield 51%, oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65 (s, 1H, 4-*H*), 7.56 (s, 2H, 5,7-2*H*), 6.85 (s, 2H, 3′,5′-2*H*), 6.11 (t, 1H, J = 6.3 Hz, CH_2CH), 4.93–4.96 (m, 2H, CH_2CH_2), 4.59 (d, 2H, J = 6.3 Hz, $CHCH_2$), 4.40–4.43 (m, 2H, CH_2CH_2). Anal. Calcd. for $C_{19}H_{12}Cl_4F_3NO_4$: C, 44.13; H, 2.34; N, 2.71. Found: C, 43.03; H, 2.41; N, 2.76.

4.1.5. Syntheses of 2-(3-(2,6-dichloro-4-(3,3-dichloroallyloxy)phenoxy)propoxy)-6-(trifluoromethyl)benzo[d]oxazole (**5e**)

Yield 52%, oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.62 (s, 1H, 4-*H*), 7.55 (s, 2H, 5,7-2*H*), 6.84 (s, 2H, 3′,5′-2*H*), 6.11 (t, 1H, J = 6.3 Hz, CH_2CH), 4.92 (t, 2H, J = 6.3 Hz, $CH_2CH_2CH_2$), 4.58 (d, 2H, J = 6.3 Hz, $CHCH_2$), 4.16 (t, 2H, J = 5.7 Hz, $CH_2CH_2CH_2$), 2.37–2.41 (m, 2H, $CH_2CH_2CH_2$). Anal. Calcd. for $C_{20}H_{14}Cl_4F_3NO_4$: C, 45.23; H, 2.66; N, 2.64. Found: C, 45.18; H, 2.59; N, 2.71.

4.1.6. Syntheses of 2-(4-(2,6-dichloro-4-(3,3-dichloroallyloxy)phenoxy)butoxy)-6-(trifluoromethyl)benzo[d]oxazole (**5f**)

Yield 27%, oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.62 (s, 1H, 4-*H*), 7.54 (s, 2H, 5,7-2*H*), 6.84 (s, 2H, 3′,5′-2*H*), 6.11 (t, 1H, J = 6.3 Hz, CH_2CH), 4.72 (t, 2H, J = 6.3 Hz, $CH_2CH_2CH_2CH_2$), 4.58 (d, 2H, J = 6.3 Hz, $CHCH_2$), 4.03 (t, 2H, J = 6.3 Hz, $CH_2CH_2CH_2CH_2$), 2.19–2.36 (m, 2H, $CH_2CH_2CH_2CH_2$), 1.99–2.05 (m, 2H, $CH_2CH_2CH_2CH_2$).

Anal. Calcd. for $C_{21}H_{16}Cl_4F_3NO_4$: C, 46.27; H, 2.96; N, 2.57. Found: C, 46.16; H, 2.91; N, 2.66.

*4.1.7. Syntheses of 2-(2,6-dichloro-4-(3,3-dichloroallyloxy)phenoxy)-5-(trifluoromethyl)benzo[*d*]oxazole (**5g**)*

Yield 36%, mp: 63–65 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.82 (s, 1H, 7-*H*), 7.60 (s, 2H, 4,6-2*H*), 7.02 (s, 2H, 3′,5′-2*H*), 6.19 (t, 1H, *J* = 6.3 Hz, CH_2CH), 4.70 (d, 2H, *J* = 6.3 Hz, $CHCH_2$). Anal. Calcd. for $C_{17}H_8Cl_4F_3NO_3$: C, 43.16; H, 1.70; N, 2.96. Found: C, 43.28; H, 1.63; N, 3.01.

*4.1.8. Syntheses of 2-(2-(2,6-dichloro-4-(3,3-dichloroallyloxy)-phenoxy)ethoxy)-5-(trifluoromethyl)benzo[*d*]oxazole (**5h**)*

Yield 29%, oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.75 (s, 1H, 7-*H*), 7.48 (s, 2H, 4,6-2*H*), 6.85 (s, 2H, 3′,5′-2*H*), 6.11 (t, 1H, *J* = 6.3 Hz, CH_2CH), 4.92–4.95 (m, 2H, CH_2CH_2), 4.59 (d, 2H, *J* = 6.3 Hz, $CHCH_2$), 4.40–4.43 (m, 2H, CH_2CH_2). Anal. Calcd. for $C_{19}H_{12}Cl_4F_3NO_4$: C, 44.13; H, 2.34; N, 2.71. Found: C, 44.26; H, 2.23; N, 2.68.

*4.1.9. Syntheses of 2-(3-(2,6-dichloro-4-(3,3-dichloroallyloxy)-phenoxy)propoxy)-5-(trifluoromethyl)benzo[*d*]oxazole (**5i**)*

Yield 35%, mp: 46–47 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.75 (s, 1H, 7-*H*), 7.42–7.46 (m, 2H, 4,6-2*H*), 6.84 (s, 2H, 3′,5′-2*H*), 6.11 (t, 1H, *J* = 6.3 Hz, CH_2CH), 4.91 (t, 2H, *J* = 6.3 Hz, $CH_2CH_2CH_2$), 4.58 (d, 2H, *J* = 6.3 Hz, $CHCH_2$), 4.16 (t, 2H, *J* = 5.7 Hz, $CH_2CH_2CH_2$), 2.35–2.42 (m, 2H, $CH_2CH_2CH_2$). Anal. Calcd. for $C_{20}H_{14}Cl_4F_3NO_4$: C, 45.23; H, 2.66; N, 2.64. Found: C, 45.30; H, 2.68; N, 2.58. LC–MS (*m*/*z* %): 532.5 $[M+H]^+$.

*4.1.10. Syntheses of 2-(4-(2,6-dichloro-4-(3,3-dichloroallyloxy)-phenoxy)butoxy)-5-(trifluoromethyl)benzo[*d*]oxazole (**5j**)*

Yield 29%, mp: 49–50 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (s, 1H, 4-*H*), 7.44–7.46 (m, 2H, 5,7-2*H*), 6.85 (s, 2H, 3′,5′-2*H*), 6.11 (t, 1H, *J* = 6.3 Hz, CH_2CH), 4.71 (t, 2H, *J* = 6.3 Hz, $CH_2CH_2CH_2CH_2$), 4.59 (d, 2H, *J* = 6.3 Hz, $CHCH_2$), 4.04 (t, 2H, *J* = 6.0 Hz, $CH_2CH_2CH_2CH_2$), 2.13–2.30 (m, 2H, $CH_2CH_2CH_2CH_2$), 1.97–2.09 (m, 2H, $CH_2CH_2CH_2CH_2$). Anal. Calcd. for $C_{21}H_{16}Cl_4F_3NO_4$: C, 46.27; H, 2.96; N, 2.57. Found: C, 46.19; H, 3.06; N, 2.52.

Acknowledgments

The project was supported by the National Key Technology Support Program during the 12th Five-Year Plan Period of China (Grant No. 2011BAE06B00, 2011BAE06B01, 2011BAE06B02, 2011BAE06B03, 2011BAE06B05) and the National Key Basic Research Program of China (973 Program) (Grant No. 2010CB126105 and 2012CB724501).

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jfluchem.2013.09.003.

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