

HETEROCYCLES, Vol. 96, No. 8, 2018, pp. 1453 - 1462. © 2018 The Japan Institute of Heterocyclic Chemistry
Received, 19th June, 2018, Accepted, 11th July, 2018, Published online, 26th July, 2018
DOI: 10.3987/COM-18-13944

SYNTHESIS AND BIOACTIVITIES EVALUATION OF NOVEL *N*-PYRIDYLPYRAZOLE DERIVATIVES WITH 1,2,3-TRIAZOLE AND QUINAZOLIN-4(3*H*)-ONE SUBSTRUCTURES

Wei Wei,³ Liangliang Zhu,¹ Yunyun Zhou,^{1*} and Zhengming Li^{2*}

¹ State Key Laboratory of Molecular Engineering of Polymers, Department of Macromolecular Science, Fudan University, Songhu Road No. 2005, Shanghai, 200433, China. ² State Key Laboratory of Elemento-Organic Chemistry, Institute of Elemento-Organic Chemistry, College of Chemistry, Nankai University, No. 94, Weijin Road, Nankai District, Tianjin 300071, China. ³ WuXi AppTec (Tian Jin) Co., Ltd., 168 Nan Hai Road, Tianjin, 300457, China. E-mail: nkzml@vip.163.com (Z. Li); zhouyunyun@fudan.edu.cn (Y. Zhou)

Abstract – Two series of *N*-pyridylpyrazole derivatives containing 1,2,3-triazole and quinazolin-4(3*H*)-one substructures were designed and synthesized. In total, 18 novel compounds were prepared, and all compounds were characterized by ¹H NMR, ¹³C NMR and elemental analysis (EA). Preliminary bioassay results revealed that a few of new compounds with quinazolin-4(3*H*)-one moiety exhibited good insecticidal activity against the oriental armyworm (*Mythimna separata*). In addition, the compounds **Ia-h** with 1, 2, 3-triazole moiety showed broad-spectrum antifungal activities against *Fusarium oxysporum f.sp.cucumerinum*, *Cercospora arachidicola* Hori, *Botryosphaeria dothidea*, *Alternaria solani*, *Gibberella zeae* and *Phytophthora capsici* at 50 µg/mL concentration. The EC₅₀ values of **Ib** and **If** against *Botryosphaeria dothidea* were 13.9 and 11.0 µg/mL, respectively, which were comparable to Chlorothalonil. These results indicated the potential application of *N*-pyridylpyrazole derivatives as fungicide in further study.

Anthranilic diamides derivatives are a couple of newly found insecticides with a unique mode of action.¹ Chlorantraniliprole, developed by the DuPont, is a representative compound among anthranilic diamides.² Due to its exceptional broad-spectrum activity, low mammalian toxicity and new mode of action, it has

attracted a lot of attentions as soon as it appeared on the market.³ By structural modifications of Chlorantraniliprole,⁴ many new compounds with excellent bioactivities have been developed.

1,2,3-Triazoles are regarded as an important heterocyclic scaffold that has been widely used in pesticide design and drug discovery. Molecules bearing the triazole structures displayed diverse biological activities such as antifungal, anticancer, antimalarial and antiviral activities.⁵ Moreover, the properties of amide moiety and 1,2,3-triazole are similarity in their size (distance between substituents was 3.8-3.9 Å and 5.0-5.1 Å in amides and triazoles, respectively), dipolar character (4 Debye and 5 Debye in amides and triazoles, respectively) and the H-bond acceptor capacity (Figure 1).⁶ As bioisosteres of the amide moiety, 1,2,3-triazole has been used in structural modification to improve the bioactivities.

Quinazolinone is another frequently encountered heterocyclic compound with a wide range of biological activities, such as antifungal, antiviral, insecticidal, and herbicidal.⁷ In our previous work, a series of *N*-pyridylpyrazole derivatives containing 2,3-dihydroquinazolin-4(1*H*)-one was designed and synthesized. The bioassay results showed that some of the compounds exhibited good insecticidal activity.⁸

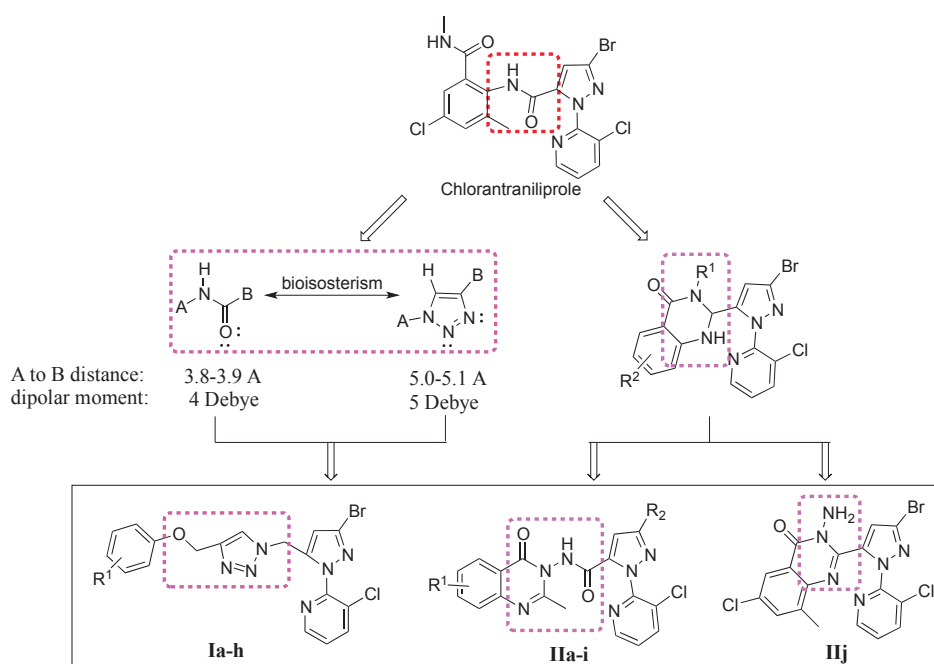
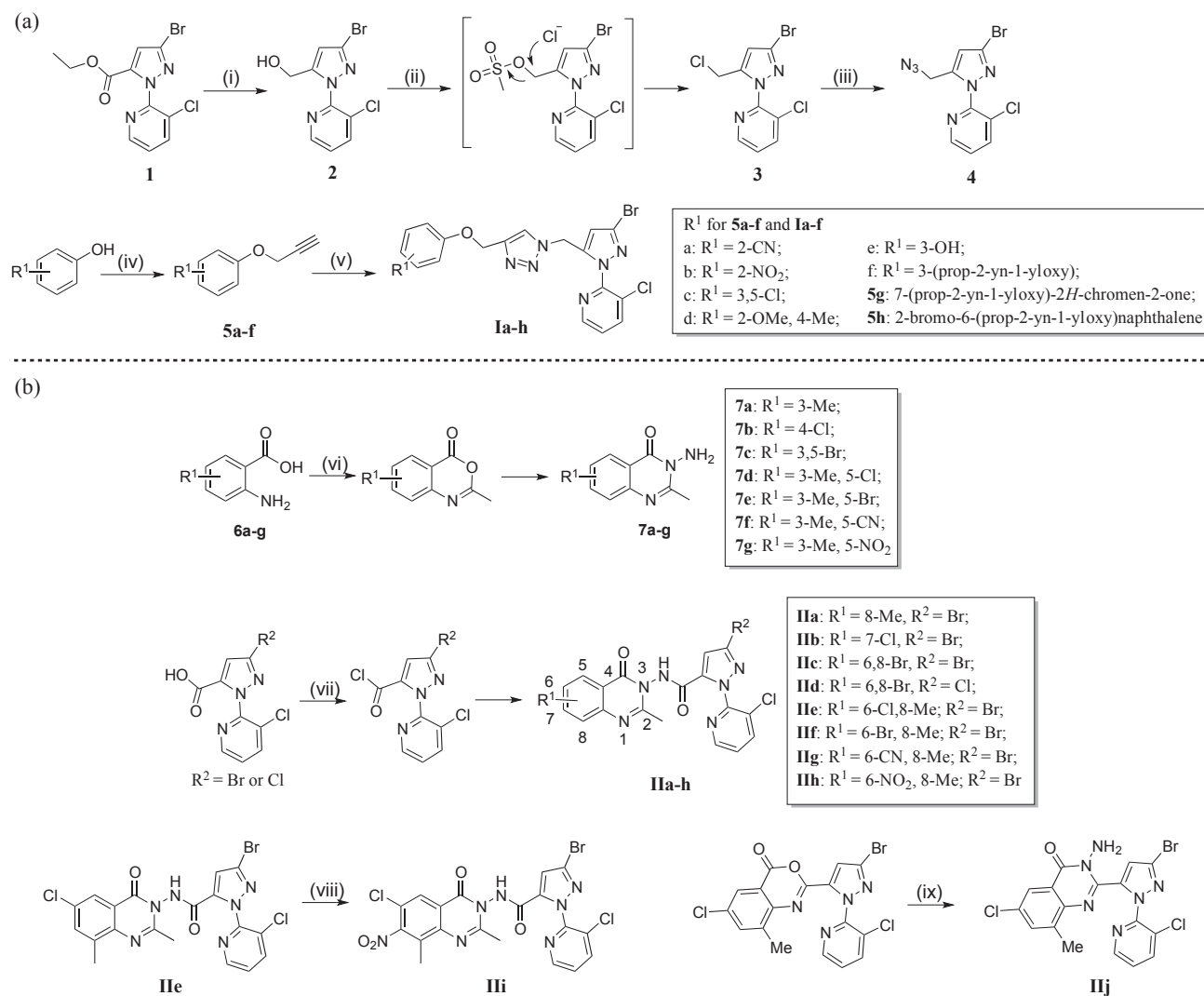


Figure 1. Design of the title compound **Ia-h** and **IIa-j**

In view of the broad-spectrum of biological activities associated with 1,2,3-triazole and quinazolinone moiety, it was attractive to merge such important biological moieties with *N*-pyridylpyrazole into a single molecular platform to produce new heterocyclic compounds and to explore their biological activities. Under the guidance of this perspective, two series of *N*-pyridylpyrazolecarboxamide derivatives containing 1,2,3-triazole and quinazolin-4(3*H*)-one were designed and synthesized, respectively, and their

larvicidal activities against oriental armyworms and their fungicidal activities *in vitro* against six plant pathogenic fungi were evaluated. On this basis, the preliminary structure–activity relationship (SAR) were also discussed.



Scheme 1. Synthesis of target compounds **Ia-h** and **IIa-j**. Reagents and conditions: (i) LiAlH₄, THF, 0 °C to rt; (ii) MeSO₂Cl, 1,2-dichloroethane, reflux; (iii) NaN₃, DMF, reflux; (iv) 3-bromopropyne, K₂CO₃, acetone, reflux; (v) CuI, THF/H₂O (v/v = 1/1), reflux; (vi) acetic anhydride, 150 °C for 4 h; NH₂NH₂·H₂O (80%), EtOH, reflux; (vii) oxalyl chloride, DMF, CH₂Cl₂; **7a-g**, Et₃N, toluene, reflux; (viii) H₂SO₄, HNO₃, rt; (ix) NH₂NH₂·H₂O (80%), EtOH, reflux.

The target compounds **Ia-h** were synthesized according to the methods shown in **Scheme 1(a)**. Compound **2** was obtained by using LiAlH₄ as the reducing agents at a low temperature. Since NaN₃ cannot react with hydroxyl directly, methanesulfonyl group was introduced to improve the reactivity. However, as methanesulfonyl was an easy leaving group, the methanesulfonyl ester intermediate was

further substituted by chloride in situ under reaction conditions to yield an alkyl chloride product. The structure of **3** was confirmed by ^1H NMR. Compound **4** was obtained by treating **3** with excess NaN_3 using DMF as solvent under reflux condition. Different substituted phenols were refluxed with 3-bromopropyne in acetone to give their corresponding propargyl ether derivatives **5a-f** in high yield.⁹ In the final step, 1,2,3-triazole ring was obtained smoothly by Huisgen cycloaddition in a regioselective way with CuI as the catalyst.¹⁰

The title compounds **IIa-j** were synthesized, as shown in **Scheme 1(b)**. **6a-g** were converted to acetylanthranil by heated in acetic anhydride,¹¹ and then the intermediate was refluxed in ethanol with $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$ (80%) to afford compounds **7a-g**.¹² 3-Bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carboxylic acid was converted to acyl chloride under the treatment of oxalyl chloride before coupling with compounds **7a-g** in the presence of Et_3N in toluene under reflux. Compound **III** was obtained by the nitration of **IIe** in good yield. Moreover, compound **IIj** was also synthesized in order to investigate the influence of the pyridylpyrazole moiety with different positions on bioactivities.

The larvicidal activity of title compounds **Ia-h**, **IIa-j** and commercial chlorantraniliprole against *M. separate* were shown in **Table 1**. Most compounds showed moderate insecticidal activities at test concentrations. In general, the compounds **IIa-j** showed a bit higher insecticidal activities than compounds **Ia-h**. Specifically, compound **If** with propynyloxy on the *meta*-position of benzene ring exhibited 40% mortality at tested concentration. And compound **IIa** and **IIb** with quinazolin-4(3*H*)-one moiety displayed 83.3% mortality at 200 $\mu\text{g}/\text{mL}$ concentration, better than the other compounds. Activities varied slightly long with the substituents changed on the 3-position of pyrazole, namely the compound with 3-Br (**IIc**) displayed higher insecticidal activity than the one with 3-Cl (**IIId**). The larvicidal activity of nitration product **III** showed 26.7% at the concentration of 200 $\mu\text{g}/\text{mL}$, lower than that of **IIe**, indicating that the introduction of nitro group has a negative effect. The compound **IIj** also exhibited less effective than **IIe**, indicating that the position of the pyridylpyrazole moiety on the quinazolin-4(3*H*)-one ring also has a negative influence on larvicidal activity. The LC_{50} of chlorantraniliprole against *M. separate* was 66.2 $\mu\text{g}/\text{mL}$,^{4f} which was much efficient than the target compounds. Overall, these results illustrated the change of amide bridge part in anthranilic diamides compounds would have significant effects on their insecticidal activity.

Table 1. Insecticidal activities of target compounds **Ia-h** and **IIa-j**

Comp.	Insecticidal activity (200 $\mu\text{g}/\text{mL}$, %)	Comp.	Insecticidal activity (200 $\mu\text{g}/\text{mL}$, %)
Ia	10	IIb	83.3

Ib	16.7	IIc	36.7
Ic	30	II d	30
Id	20	II e	36.7
Ie	16.7	II f	20
If	40	II g	13.3
Ig	20	II h	53.3
Ih	10	II i	26.7
IIa	83.3	II j	20
control^a	100	control^a	100

^a Chlorantraniliprole

Considering the various bioactivities of 1,2,3-triazole and quinazolin-4(3*H*)-one moieties, we also investigated the antifungal activities of the target compounds. The antifungal activities of compounds **Ia-h** and **IIa-j** against *F. oxysporum f.sp.cucumerinum*, *C. arachidicola* Hori, *B. dothidea*, *A. solani*, *G. zea*e and *P. capsici* *in vitro* were summarized in **Table 2** and the fungicidal effects, the contrast diagram of selected compounds and control were shown in **Figure 2**. By comparison, it was found that at the concentration of 50 µg/mL, compounds with the triazole moiety showed much higher inhibitory activities as compare to the quinazolin-4(3*H*)-one moiety. The fungicidal activities of compounds **Ia-h** with the triazole showed broad potency against the tested fungi and they were even comparable to that of chlorothalonil. On the *B. dothidea* strain, the compounds **Ib-f** and **Ih** were more active than the control. For *C. arachidicola* Hori, the inhibitory rates of compounds **Ib-f** and **Ih** were 53.8%, which was close to the control (56.8%). Compounds **Ib**, **Ic**, and **If** also exhibited high antifungal activity of *A. solani*. On the other hand, Compounds **IIa-j** exhibited moderate to good activities for some of the tested fungi. Among them, the compound **IIc** showed 41.7% and 92.9% inhibitory rates for *C. arachidicola* Hori and *B. dothidea*, equal to the control compound. However, they were not very sensitive against *G. zea*e and *P. capsici* and only compound **IIa**, **IIh** and **IIi** showed moderate fatality rate (52.4%, 57.1% and 52.4%, respectively). The toxicity profile (EC₅₀ values) of compounds **Ib** and **If** was shown in **Table 3**. The EC₅₀ values of **Ib** and **If** against *Botryosphaeria dothidea* were 13.9 and 11.0 µg/mL, respectively, which were comparable to that of Chlorothalonil (7.3 µg/mL).

We would like to emphasize that, among these compounds, **Ib** and **If** showed excellent inhibitory rates of the four tested fungi, which can be used as lead compound for the further study. These results indicated that the introduction of triazole ring significantly improved the antifungal activities of these compounds, and expanded the scope of the study on the bioactivity.

Table 2. Antifungal activities of target compounds **Ia-h** and **IIa-j**

Comp.	Fungicidal inhibition (50 µg/mL, %)					
	<i>Fusarium oxysporum f.sp.cucumerinum</i>	<i>Cercospora arachidicola</i> Hori	<i>Botryosphaeria dothidea</i>	<i>Alternaria solani</i>	<i>Gibberella zeae</i>	<i>Phytophthora capsici</i>
Ia	57.9	46.2	84.6	47.1	17.2	28.6
Ib	84.2	53.8	92.3	58.8	37.9	0
Ic	73.7	53.8	92.3	58.8	34.5	23.8
Id	73.7	53.8	92.3	35.3	37.9	19
Ie	52.6	53.8	92.3	17.6	20.7	42.9
If	78.9	53.8	92.3	58.8	51.7	19
Ig	63.2	53.8	69.2	35.3	24.1	19
Ih	63.2	53.8	92.3	47.1	44.8	14.3
IIa	31.6	16.7	78.6	21.4	19	52.4
IIb	15.8	33.3	64.3	21.4	42.9	47.6
IIc	42.1	41.7	92.9	28.6	28.6	28.6
IId	31.6	25	64.3	28.6	23.8	23.8
IIe	15.8	16.7	21.4	21.4	23.8	33.3
IIf	15.8	25	35.7	21.4	28.6	42.9
IIg	15.8	8.3	35.7	14.3	33.3	38.1
IIh	26.3	8.3	28.6	21.4	33.3	57.1
IIi	10.5	0	35.7	28.6	38.1	52.4
IIj	15.8	16.7	35.7	35.7	23.8	19
control^b	82.9	56.8	87.6	63.6	73.1	80.6

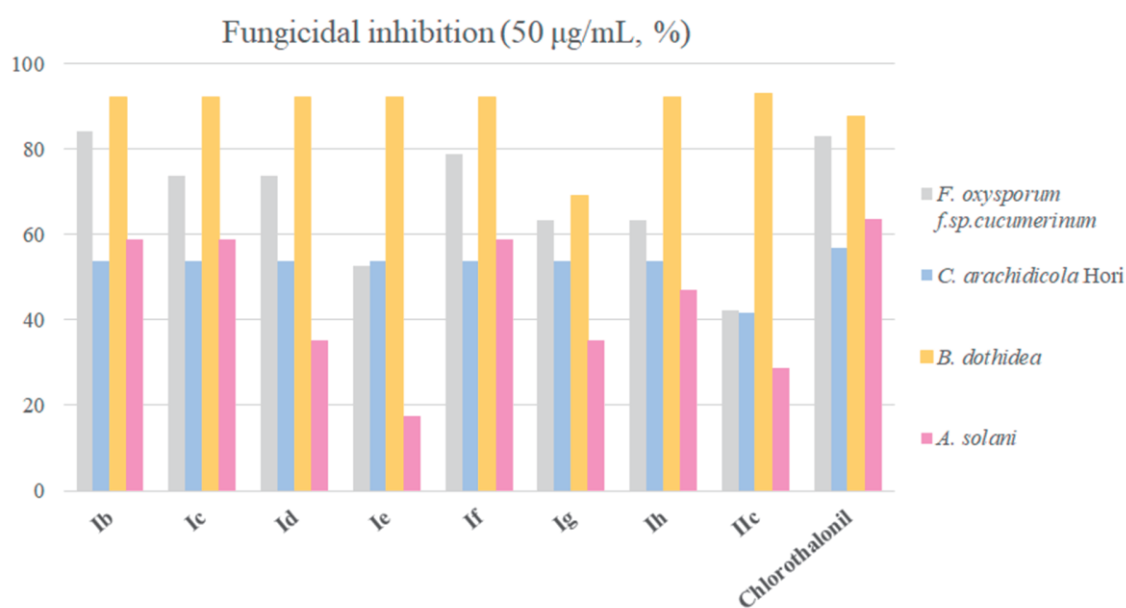
^b Chlorothalonil**Figure 2.** The *in vitro* fungicidal activity of compounds **Ib-h**, **IIc** and chlorothalonil against *F. oxysporum f.sp.cucumerinum*, *C. arachidicola* Hori, *B. dothidea* and *A. solani* at 50 µg/mL (% inhibition)

Table 3. The EC₅₀ values of antifungal activities of the target compounds **Ib** and **If**

Compound	Fungi	Toxicity equation	Correlation coefficient (R^2)	EC ₅₀ (μg/mL)
Ib	<i>Fusarium oxysporum</i> <i>f.sp.cucumerinum</i>	$y = 2.1575x + 2.1544$	0.9900	20.8
	<i>Cercospora arachidicola</i> Hori	$y = 1.1102x + 3.2211$	0.9965	40.0
	<i>Botryosphaeria dothidea</i>	$y = 2.2357x + 2.4399$	0.9878	13.9
	<i>Alternaria solani</i>	$y = 1.3364x + 2.9308$	0.9940	35.3
	<i>Fusarium oxysporum</i> <i>f.sp.cucumerinum</i>	$y = 1.9239x + 2.4124$	0.9873	22.1
If	<i>Cercospora arachidicola</i> Hori	$y = 0.7967x + 3.8213$	0.9857	30.1
	<i>Botryosphaeria dothidea</i>	$y = 1.8890x + 3.0314$	0.9802	11.0
	<i>Alternaria solani</i>	$y = 1.3364x + 2.8840$	0.9951	38.3
	<i>Fusarium oxysporum</i> <i>f.sp.cucumerinum</i>	$y = 1.2151x + 4.8806$	0.9851	1.2
Chlorothalonil	<i>Cercospora arachidicola</i> Hori	$y = 1.3220x + 3.5711$	0.9565	12.0
	<i>Botryosphaeria dothidea</i>	$y = 1.3890x + 3.7981$	0.9862	7.3
	<i>Alternaria solani</i>	$y = 1.0258x + 3.7715$	0.9769	15.7

In conclusion, two series of *N*-pyridylpyrazole derivatives were designed and synthesized by modification of the amide bridge part. The obtained novel target compounds were comprehensively characterized by ¹H NMR, ¹³C NMR and EA. Their biological activities were also evaluated. Although the preliminary insecticidal activity tests showed that most compounds showed moderate mortality rates against *M. separate* at the concentration of 200 μg/mL, the antifungal tests demonstrated that compounds **Ia-h** exhibited excellent activities against the tested fungi at the concentration of 50 μg/mL *in vitro*. The compounds **Ib** and **If** exhibited excellent antifungal activities against *Botryosphaeria dothidea*, with EC₅₀ values of 13.9 and 11.0 μg/mL, respectively, which were comparable to Chlorothalonil. These results enlighten us to make further efforts on structural optimization of novel anthranilic diamides and to explore the potential applications in antifungal fields.

EXPERIMENTAL

Materials and Instruments. All the reagents were of analytical grade. Melting points of all the compounds were determined on an X-4 binocular micro-scope (Gongyi Tech. Instrument Co., Henan,

China) and without corrected. ^1H and ^{13}C Nuclear magnetic resonance (NMR) spectra were obtained on a Bruker AV-400 spectrometer (400 MHz) with tetramethylsilane (TMS) as the internal standard. Elemental analyses (EA) were measured on a Yanaco CHN Corder MF-3 automatic elemental analyzer. High resolution mass spectrometry (HRMS) data was measured using a Matrix Assisted Laser Desorption Ionization-Time of Flight/Time of Flight Mass Spectrometer (5800). Column chromatography purification was carried out using silica gel (200–300 mesh).

Synthesis route. The synthesis route for title compounds **Ia-h** and **IIa-j** was shown in **Scheme 1**. Key intermediate **4** was prepared from the starting material ethyl 3-bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carboxylate. Compounds **7a-g** were prepared by treating different substituted 2-aminobenzoic acid with acetic anhydride, then followed by 80% hydrazine hydrate in EtOH under reflux condition. Detailed synthetic procedures and spectral data for title compounds **Ia-h**, **IIa-j** and intermediates were given in the Supporting Information.

Bioassays. Larvicidal activity of compounds **Ia-h** and **IIa-j** against *M. separata* was performed on testing organism reared in greenhouse. The bioassay was reduplicative at 25 ± 1 °C according to the requirements of statistics. Evaluation results were got by a dead/alive basis, and death rates were corrected by applying Abbott's formula¹³ with chlorantraniliprole used as positive control. Antifungal activities of compounds **Ia-h** and **IIa-j** against *F. oxysporum f. sp. cucumerinum*, *C. arachidicola* Hori, *B. dothidea*, *A. solani*, *G. zaeae* and *P. capsici in vitro* were tested *via* mycelium growth rate method as referring to the literature.⁴⁰ Chlorothalonil was used as the positive control.

ACKNOWLEDGEMENTS

This work was supported by the NSFC/China (21502229).

REFERENCES

1. G. P. Lahm, T. P. Selby, J. H. Freudenberger, T. M. Stevenson, B. J. Myers, G. Seburyamo, B. K. Smith, L. Flexner, C. E. Clark, and D. Cordova, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 4898.
2. G. P. Lahm, T. M. Stevenson, T. P. Selby, J. H. Freudenberger, D. Cordova, L. Flexner, C. A. Bellin, C. M. Dubas, B. K. Smith, K. A. Hughes, J. G. Hollingshaus, C. E. Clark, and E. A. Benner, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 6274.
3. (a) G. P. Lahm, D. Cordova, and J. D. Barry, *Bioorg. Med. Chem.*, 2009, **17**, 4127; (b) T. P. Selby, G. P. Lahm, T. M. Stevenson, K. A. Hughes, D. Cordova, I. B. Annan, J. D. Barry, E. A. Benner, M. J. Currie, and T. F. Pahutski, *Bioorg. Med. Chem. Lett.*, 2013, **23**, 6341; (c) X.-H. Lv, J.-J. Xiao, Z.-L. Ren, M.-J. Chu, P. Wang, X.-F. Meng, D.-D. Li, and H.-Q. Cao, *RSC Adv.*, 2015, **5**, 55179; (d) D.-P. Jiang, C.-C. Zhu, X.-S. Shao, J.-G. Cheng, and Z. Li, *Chin. Chem. Lett.*, 2015, **26**, 662.

4. (a) Q. Liu, R. Zhu, S. Gao, S.-H. Ma, H.-J. Tang, J.-J. Yang, Y.-M. Diao, H.-L. Wang, and H.-J. Zhu, *Pest Manag. Sci.*, 2017, **73**, 917; (b) J. Wu, B.-A. Song, D.-Y. Hu, M. Yue, and S. Yang, *Pest Manag. Sci.*, 2012, **68**, 801; (c) Y. Zhou, B. Wang, F. Di, L. Xiong, N. Yang, Y. Li, Y. Li, and Z. Li, *Bioorg. Med. Chem. Lett.*, 2014, **24**, 2295; (d) S. Zhou, S. Zhou, X. Hua, W. Wei, Y. Xie, M. Chen, X. Meng, M. Liu, L. Xiong, N. Yang, B. Wang, and Z. Li, *Chin. J. Chem.*, 2016, **34**, 1218; (e) R. Zhang, K. Liu, Y. Cui, W. Zhang, L. He, S. Guo, Y. Chen, Q. X. Li, S. Liu, and B. Wang, *RSC Adv.*, 2015, **5**, 35874; (f) S. Zhou, S. Zhou, Y. Xie, X. Meng, B. Wang, L. Xiong, N. Yang, and Z. Li, *Chin. Chem. Lett.*, 10.1016/j.ccllet.2017.10.022; (g) Q. Feng, Z.-L. Liu, L.-X. Xiong, M.-Z. Wang, Y.-Q. Li, and Z.-M. Li, *J. Agric. Food Chem.*, 2010, **58**, 12327; (h) S. A. Kon'Kov, K. S. Krylov, K. M. Bormasheva, and I. K. Moiseev, *Rus. J. Org. Chem.*, 2014, **50**, 1636; (i) J.-B. Liu, Y.-X. Li, X.-L. Zhang, X.-W. Hua, C.-C. Wu, W. Wei, Y.-Y. Wan, D.-D. Cheng, L.-X. Xiong, N. Yang, H.-B. Song, and Z.-M. Li, *J. Agric. Food Chem.*, 2016, **64**, 3697; (j) X. Zhang, Y. Li, J. Ma, H. Zhu, B. Wang, M. Mao, L. Xiong, Y. Li, and Z. Li, *Bioorg. Med. Chem.*, 2014, **22**, 186; (k) Y. Zhao, Y. Li, L. Xiong, H. Wang, and Z. Li, *Chin. J. Chem.*, 2012, **30**, 1748; (l) Y.-B. Chen, J.-L. Li, X.-S. Shao, X.-Y. Xu, and Z. Li, *Chin. Chem. Lett.*, 2013, **24**, 673; (m) J.-J. Shi, G.-H. Ren, N.-J. Wu, J.-Q. Weng, T.-M. Xu, X.-H. Liu, and C.-X. Tan, *Chin. Chem. Lett.*, 2017, **28**, 1727; (n) Z.-B. Wu, X. Zhou, Y.-Q. Ye, P.-Y. Wang, and S. Yang, *Chin. Chem. Lett.*, 2017, **28**, 121; (o) X. Hua, W. Mao, Z. Fan, X. Ji, F. Li, G. Zong, H. Song, K. Tatiana, Y. Y. Morzherin, N. P. Belskaya, and V. A. Bakulev, *J. Heterocycl. Chem.*, 2016, **53**, 865.
5. (a) Z.-C. Dai, Y.-F. Chen, M. Zhang, S.-K. Li, T.-T. Yang, L. Shen, J.-X. Wang, S.-S. Qian, H.-L. Zhu, and Y.-H. Ye, *Org. Biomol. Chem.*, 2015, **13**, 477; (b) L.-Y. Zhang, B.-L. Wang, Y.-Z. Zhan, Y. Zhang, X. Zhang, and Z.-M. Li, *Chin. Chem. Lett.*, 2016, **27**, 163; (c) H. Tang, C.-H. Zheng, X.-H. Ren, J. Liu, N. Liu, J.-G. Lv, J. Zhu, and Y.-J. Zhou, *Chin. Chem. Lett.*, 2013, **24**, 219; (d) K. Pyta, M. Blecha, A. Janas, K. Klich, P. Pecyna, M. Gajecka, and P. Przybylski, *Bioorg. Med. Chem. Lett.*, 2016, **26**, 4322; (e) S. M. Hashemi, H. Badali, H. Irannejad, M. Shokrzadeh, and S. Emami, *Bioorg. Med. Chem.*, 2015, **23**, 1481; (f) M. Mao, Y. Li, Q. Liu, L. Xiong, X. Zhang, and Z. Li, *J. Pestic. Sci.*, 2015, **40**, 138.
6. E. D. Chrysina, É. Bokor, K.-M. Alexacou, M.-D. Charavgi, G. N. Oikonomakos, S. E. Zographos, D. D. Leonidas, N. G. Oikonomakos, and L. Somsák, *Tetrahedron: Asymmetry*, 2009, **20**, 733.
7. (a) K. Veena Vani, G. Ramesh, and C. Venkata Rao, *J. Heterocycl. Chem.*, 2016, **53**, 719; (b) A. A. Al-Amiery, A. A. H. Kadhum, M. Shamel, M. Satar, Y. Khalid, and A. B. Mohamad, *Med. Chem. Res.*, 2014, **23**, 236; (c) M. M. Aly, Y. A. Mohamed, K. A. M. El-Bayouki, W. M. Basyouni, and S. Y. Abbas, *Eur. J. Med. Chem.*, 2010, **45**, 3365; (d) U. A. Kshirsagar, *Org. Biomol. Chem.*, 2015, **13**, 9336; (e) M. M. Elshahawi, A. K. El-Ziaty, J. M. Morsy, and A. F. Aly, *J. Heterocycl. Chem.*, 2016,

- 53**, 1443.
8. Y. Zhou, Q. Feng, F. Di, Q. Liu, D. Wang, Y. Chen, L. Xiong, H. Song, Y. Li, and Z. Li, *Bioorg. Med. Chem.*, 2013, **21**, 4968.
 9. (a) J. Emilio de la Cerda-Pedro, Y. A. Amador-Sánchez, M. Cortés-Hernández, J. Pérez-Pérez, S. Rojas-Lima, and H. López-Ruiz, *Heterocycles*, 2014, **89**, 27; (b) F.-T. Luo, S.-L. Ko, L. Liu, and H. Chen, *Heterocycles*, 2000, **53**, 2055; (c) T. Sugihara, A. Murakawa, C. Sawanaka, M. Seki, N. Iio, A. Iizuka, T. Oohora, and S. Honzawa, *Heterocycles*, 2012, **86**, 1039.
 10. (a) V. O. Rodionov, V. V. Fokin, and M. G. Finn, *Angew. Chem. Int. Ed.*, 2005, **44**, 2210; (b) B. T. Worrell, J. A. Malik, and V. V. Fokin, *Science*, 2013, **340**, 457; (c) F. Himo, T. Lovell, R. Hilgraf, V. V. Rostovtsev, L. Noodleman, K. B. Sharpless, and V. V. Fokin, *J. Am. Chem. Soc.*, 2005, **127**, 210.
 11. T. Nagase, T. Mizutani, S. Ishikawa, E. Sekino, T. Sasaki, T. Fujimura, S. Ito, Y. Mitobe, Y. Miyamoto, R. Yoshimoto, T. Tanaka, A. Ishihara, N. Takenaga, S. Tokita, T. Fukami, and N. Sato, *J. Med. Chem.*, 2008, **51**, 4780.
 12. (a) W. J. Watkins, L. Chong, A. Cho, R. Hilgenkamp, M. Ludwikow, N. Garizi, N. Iqbal, J. Barnard, R. Singh, D. Madsen, K. Lolans, O. Lomovskaya, U. Oza, P. Kumaraswamy, A. Blecken, S. Bai, D. J. Loury, D. C. Griffith, and M. N. Dudley, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 2802; (b) M. I. Marzouk, S. A. Shaker, T. A. Farghaly, M. A. El-Hashash, and S. M. Hussein, *J. Heterocycl. Chem.*, 2017, **54**, 3331; (c) X. Wang, C.-h. Tang, G.-l. Wei, and J.-f. Long, *J. Heterocycl. Chem.*, 2017, **54**, 3220.
 13. W. S. Abbott, *J. Econ. Entomol.*, 1925, **18**, 265.