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Original article

Design, synthesis and antifungal activities of novel pyrrole alkaloid analogs

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ABSTRACT

A series of novel analogs of pyrrole alkaloid were designed and synthesized by a facile method and their structures were characterized by ^{1}H NMR, ^{13}C NMR and high-resolution mass spectrometry (HRMS). The structure of compound **2a** was identified by 2D NMR including heteronuclear multiple-quantum coherence (HMQC), heteronuclear multiple-bond correlation (HMBC) and H–H correlation spectrometry (H–H COSY) spectra. Their antifungal activities against five fungi were evaluated, and the results indicated that some of the title compounds showed moderate fungicidal activities in vitro against *Alternaria solani*, *Cercospora arachidicola*, *Fusarium omysporum*, *Gibberella zeae* and *Physalospora piricola* at the dosage of 50 μg mL^{-1}. Compound **2a** and **3a** exhibited good activities against *P. piricola* at low dosage.

1. Introduction

In the past century, a lot of bromopyrrole alkaloids had been isolated from marine organism and exhibited good biological activities [1–3]. For instance, the pyrrolomycin (**A**, Fig. 1) had distinguished antibiotic activity [4]. It was commonly assumed that many bromopyrrole alkaloid metabolites were served as a chemical protection role for the organism including antifeedant, antibacterial and antifungal agent, etc [5–7]. For example, natural product dispacamide (**B**, Fig. 1) and its derivatives isolated from sponge had evident antifeedant and antibacterial activities [7–9]. Anthranilamide (**C**, Fig. 1) isolated from a culture of marine *Streptomyces* sp. strain B7747 showed remarkable antimicroalgal activity [10]. Comparing to dispacamide, there were two similar four-membered carboxamide moieties among them (–N(CH$_3$)COCH$_2$CH$_2$– and –CONHCH$_2$CH$_2$–). Additionally, it is reported that *N*-(benzyloxy)benzamide (**D**, Fig. 1) and its analogs with the *O*-benzylhydroxylamine moiety (–CONHOCH$_2$–Ar) possessed antibacterial, herbicidal and enzyme inhibiting activities [11–14]. The pharmacophore (–CONHOCH$_2$–) was generally considered to be the bioisosteric analog (–CONHCH$_2$CH$_2$–) for drug's design [15]. Considering the potential antifungal activity of the bromopyrrole alkaloid and the activity contribution of the *O*-benzylhydroxylamine group to the *N*-(benzyloxy)benzamide derivatives [11–14], a series of new dibromopyrrole alkaloid analogs (**E**, Fig. 1) were designed, synthesized and tested against fungi in vitro. Their antifungal activities against five fungi were evaluated and the possible structure–activity relationships (SAR) were discussed. In order to study the SAR, these analogs' benzene ring was replaced with different groups. Based on the SAR, some analogs with the pyrrole ring substituted by –Cl (m = 2), –Br (m = 3) or unsubstituted by any halogen atom were also synthesized. And the pyrrole ring of some derivatives was further methylated. All the new derivatives were designed to learn whether those might increase or decrease their biological activities.

2. Chemistry

2.1. Synthesis

In this paper, 1*H*-pyrrole-2-carboxylic acid **2** was successfully synthesized through an improved procedure (see experimental Section 5.2.1 and Scheme 1). Compound **2** was failed to be given when the mixture was stirred for 10 h at room temperature according to the literature [16]. 4,5-Dichloro-1*H*-pyrrole-2-carboxylic acid **5** was also successfully synthesized using a mixture solution (see experimental Section 5.2.1 and Scheme 1). It is failed to get compound **5** when the solution was only dichloromethane and stirred for 6 h at room temperature according to the literature [17]. Compounds **3a**–**r**, **2a**, **2g**, **2r**, **4a**, **4g**, **4r**, **5a**, **5g**, **5r**, **2aa**, **2ab** were all synthesized by a facile method referencing to the literature (see experimental Section 5.2.1.4 and 5.2.1.5, Scheme 2 and Table 1) [18]. Especially, Compound **7r** was fully synthesized by a novel method described in the synthesis section. Since the reaction of bromine with 1*H*-pyrrole-2-carboxylic acid was complicated and the byproduct was difficult to separate from each other [19–23], it is unfortunately

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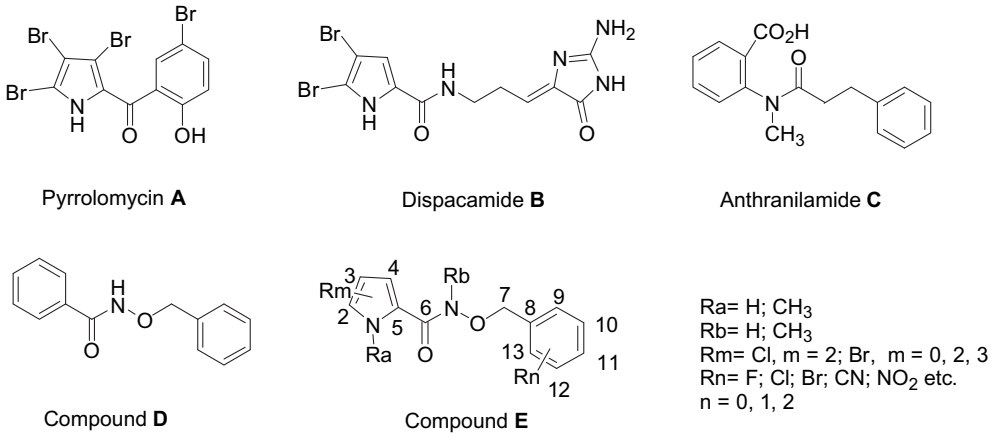


Fig. 1. Chemical structure of compounds **A**–**E**.

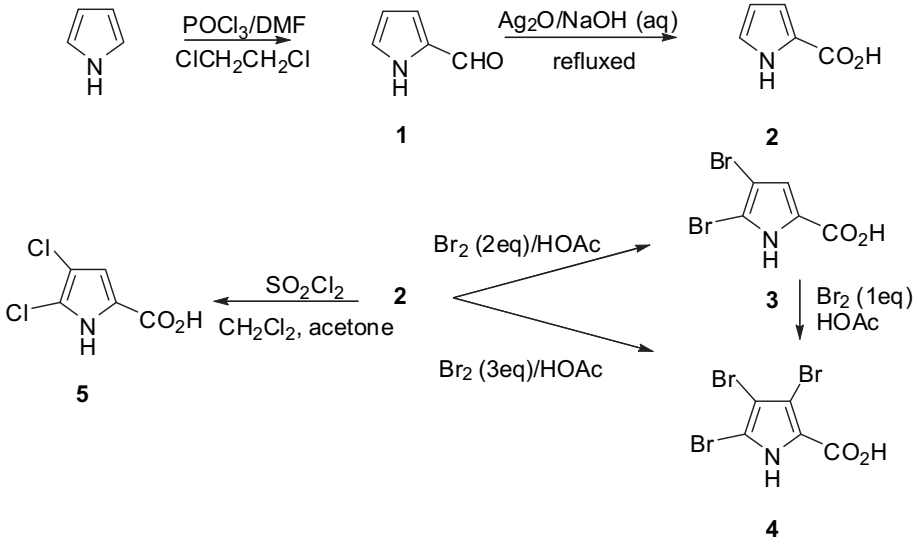
to obtain the monobromine-1*H*-pyrrole-2-carboxylic acid and corresponding target product.

2.2. Structure elucidation

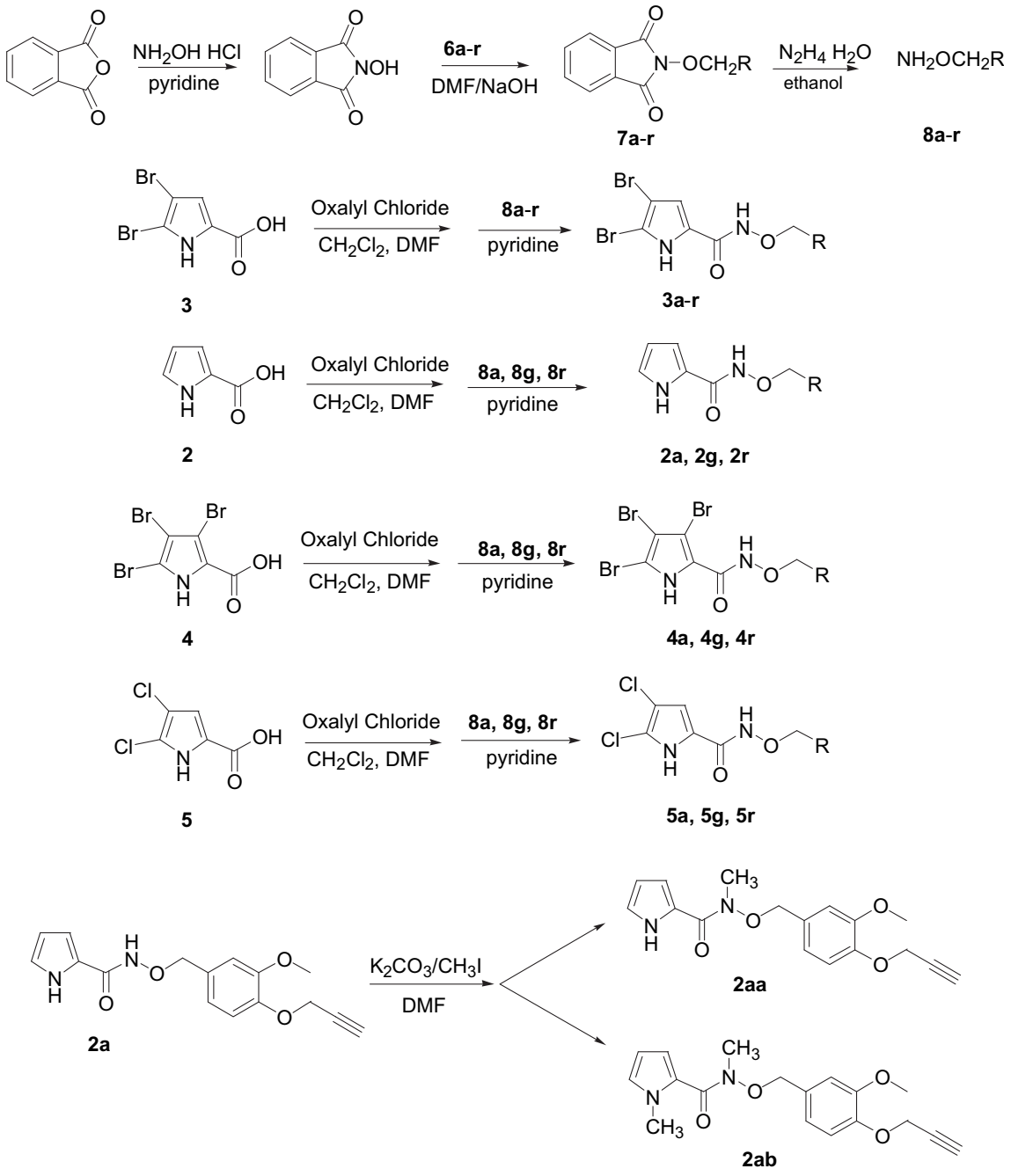
The structure of the potential compound **2a** was elucidated by 1D NMR and 2D NMR as follows: The molecular formula of **2a** was revealed as $C_{16}H_{16}N_2O_4$ by HRMS data $[M + Na]^+$ (found 323.1004, calcd 323.1002). The ^1H and ^{13}C NMR (**2a**) spectra showed the signals of six quaternary, seven CH, two CH_2 and one CH_3 carbon atoms. Considered the reagents, in the HMQC spectra showed $\delta_H = 11.58$ (s, 1H) and $\delta_H = 11.24$ (s, 1H) belonged to the Pyrrole–NH or –CONH–; $\delta_H = 7.02$ (d, 1H) and $\delta_H = 6.95$ (d, 1H) belonged to the Ar–H, which was confirmed by their *J* value ($J = 8.0$ Hz). $\delta_H = 7.10$ (s, 1H), 6.92 (s, 1H), 6.71 (s, 1H) and 6.09 (s, 1H) belonged to the Ar–H or Pyrrole–H.

Based on the HMBC and ^{13}C Dept spectra, the correlations between $\delta_H = 11.24$ (s, 1H)/$\delta_C = 159.7$ (s), $\delta_H = 4.83$ (s, 2H)/$\delta_C = 129.6$ (s), 4.79 (s, 2H)/$\delta_C = 146.4$ (s) and $\delta_H = 3.78$ (s, 3H)/$\delta_C = 148.9$ (s) indicated $\delta_H = 11.24$, 4.83, 4.79, 3.78 belonged to –CONH–, H-7, H-14, H-17 and $\delta_C = 159.7$, 129.6, 146.4, 148.9 belonged to C-6, C-8, C-11, C-10 respectively. So $\delta_H = 11.58$ (s, 1H) belonged to the Pyrrole–NH. The correlations between $\delta_H = 7.10$ (s, 1H)/C-10 ($\delta_C = 148.9$), $\delta_H = 6.92$ (s, 1H), 6.09 (s, 1H)/C-6 ($\delta_C = 159.7$) indicated $\delta_H = 7.10$ belonged to H-9 (Ar–H); $\delta_H = 6.92$, 6.09 belonged to Pyrrole–H. So $\delta_H = 6.71$ (s, 1H) belonged to the H-2. The correlations between $\delta_H = 6.95$ (d, 1H)/C-7 ($\delta_C = 77.1$) explained $\delta_H = 6.95$ belonged to H-13; so $\delta_H = 7.02$ (d, 1H) belonged to H-12. The correlations between $\delta_H = 4.79$ (H-14)/$\delta_C = 79.2$ (s), 78.2 (d); $\delta_H = 3.55$ (s, 1H)/C-14 ($\delta_C = 55.9$) indicated $\delta_H = 3.55$ and $\delta_C = 79.2$ belonged to H-16 and C-15 respectively. All the data indicated the structure of **2a** should be as follow (Fig. 2).

In the H–H COSY spectra, the correlations between $\delta_H = 6.09$ (s, 1H)/$\delta_H = 6.92$ (s, 1H) and $\delta_H = 6.09$ (s, 1H)/$\delta_H = 6.71$ (H-2) indicated $\delta_H = 6.09$, 6.92 belonged to H-3 and H-4 respectively. The correlations between $\delta_H = 11.58$ (Pyrrole–NH)/$\delta_H = 6.09$ (H-3), 6.71 (H-2), 6.92 (H-4), the correlations between $\delta_H = 7.02$ (H-12)/$\delta_H = 6.95$ (H-13) and the correlations between $\delta_H = 4.79$ (H-14)/$\delta_H = 3.55$ (H-16) further verified the positions of all the protons. Additionally, the structures of compounds **2aa** and **2ab** were also testified by 1D NMR and 2D NMR spectra.



Scheme 1. Synthetic routes to compounds **1**–**5**.



Scheme 2. Synthetic routes to compounds **7a**–**2ab**.

3. Biological results and discussion

3.1. Fungicidal activities

Table 2 showed the fungicidal activities against *Alternaria solani*, *Cercospora arachidicola*, *Fusarium omysporum*, *Gibberella zeae*, *Physalospora piricola* of the compounds **3a**–**r**, **2a**, **2g**, **2r**, **4a**, **4g**, **4r**, **5a**, **5g**, **5r**, **2aa**, **2ab**, anthranilamide and the commercial fungicide fenpiclonil at the dosage of 50 μg mL^{-1}. Table 3 showed the EC_{50} of the high fungicidal activity compounds **2a**, **3a**, and fenpiclonil.

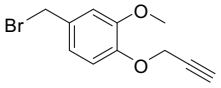
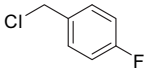
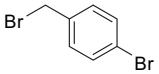
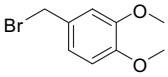
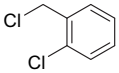
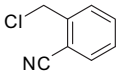
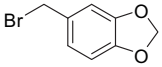
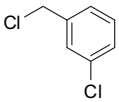
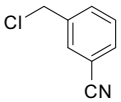
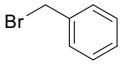
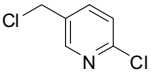
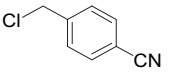
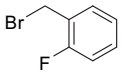
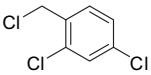
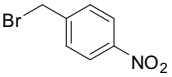
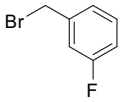
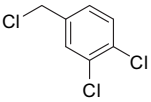
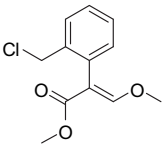
3.1.1. Fungicidal activity against A. solani

The screening data of Table 2 indicated that at the dosage of 50 μg mL^{-1}, most compounds exhibited low activities against *A. solani* except the compounds **3a**, **3b**, **3d**-**3g** and **3i**. Comparing the biological activities with the rest of the compounds', the inhibition activities of **3a**, **3b**, **3d**–**g** and **3i** were all over 60.0%. In comparison with **3d**, the results indicated that H-10 and H-11 substituted by $-OCH_3$ (**3b**) or H-13 substituted by $-F$ (**3e**) in the aroma ring would improve its fungicidal activity.

3.1.2. Fungicidal activity against C. arachidicola

The biological activity rules of **3a**–**2ab** against *C. arachidicola* were generally the same as the test against *A. solani* showed. To be pointed out, the inhibition activities of **3a**–**g** and **3i** were all over 50.0%. Comparing with **3d** and anthranilamide, the results indicated that H-10 and H-11 substituted by $-OCH_2O-$(**3c**) or H-12 substituted by $-Cl$ (**3i**) in the aroma ring would evidently increase its fungicidal activity.

Table 1
The R group in compounds of **6** (Br–CH_2R or Cl–CH_2R)-**5r**.

Compd.	R	Compd.	R	Compd.	R
6a		**6g**		**6m**	
6b		**6h**		**6n**	
6c		**6i**		**6o**	
6d		**6j**		**6p**	
6e		**6k**		**6q**	
6f		**6l**		**6r**	

3.1.3. Fungicidal activity against F. omysporum

The screening data of Table 2 indicated that at the dosage of 50 μg mL^{-1}, most compounds exhibited low activities against *F. omysporum* except the compounds **3a**, **3b**, **3d**–**g** and **3i**. The fungicidal activities of **3a**, **3b**, **3e**–**g** and **3i** were all over 40.0%. Comparing with **3d**, the test indicated that H-10 substituted by $-OCH_3$ and H-11 substituted by propargyl (**3a**) or H-11 substituted by –F (**3g**), H-12 substituted by –Cl (**3i**) in the aroma ring would enhance fungicidal activity.

3.1.4. Fungicidal activity against G. zeae

The screening data of Table 2 indicated that nearly all of the compounds (**3a**–**2ab**) exhibited low activities against *G. zeae*.

3.1.5. Fungicidal activity against P. piricola

The screening data of Table 2 indicated that the target compounds exhibited low activities against *P. piricola* except for **3a**, **3b**, **3g**, **3p** and **2a**. At the dosage of 50 μg mL^{-1}, the fungicidal activities of compounds **3a**, **3b**, **3g**, **3p** and **2a** were 90.0%, 50.0%, 55.1%, 48.1%, 100% respectively. Comparing with **3d**, the antifungal activities of compounds **3a**, **3b** and **3g** further testified their rules exhibited in other fungi. To be pointed out, the activity of compound **3p** showed that H-11 in the aroma ring was substituted by –CN would enhance its activity. The EC_{50} value of **2a** and **3a** against *P. piricola* was 4.50 μg mL^{-1} and 9.78 μg mL^{-1} respectively (Table 3), which implied that the pyrrole ring substituted by few halogen atoms and the **6a** moiety were vital for high activity against *P. piricola*.

Comparing the fungicidal activities of the series of compounds **2**, **3**, **4**, **5** against all the fungi except for **2a** against *P. piricola*, it would be found that the series of compounds **3** had a little more activities and spectrums than the **2**, **4** and **5** series, which indicated that the addition of two bromine atoms to the pyrrole ring 2 and 3 position might improve its antifungal activity. Comparing with the series of **3**, the addition of two chlorine atoms (**5a**, **5g** and **5r**) or three bromine atoms (**4a**, **4g** and **4r**) to the pyrrole ring did not increase its fungicidal activity. The biological activities of **2aa** and **2ab** against all the fungi implied that the methylated pyrrole ring might decrease their activities.

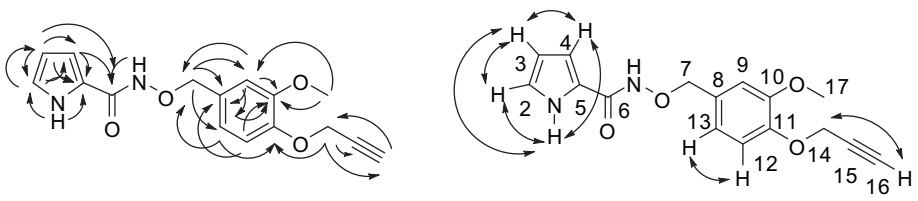


Fig. 2. Key HMBC correlations (left) and key H–H correlations (right) of **2a**.

Table 2
Fungicidal activities at dosage of 50 μg mL^{-1}.

Compd.	*A. solani*	*C. arachidicola*	*F. omysporum*	*G. zeae*	*P. piricola*
Inhibition (%)					
3a	64.9	56.3	47.1	8.7	90.0
3b	73.3	60.0	41.2	4.6	50.0
3c	31.6	75.0	23.8	14.7	18.5
3d	66.7	53.3	40.0	9.1	40.9
3e	76.2	50.3	41.2	18.2	27.3
3f	61.9	54.0	40.8	4.5	40.9
3g	66.5	62.5	58.0	21.7	55.1
3h	19.0	20.0	0	13.6	13.4
3i	66.7	80.0	47.0	17.4	38.9
3j	5.3	28.6	23.8	0	37.0
3k	21.1	35.7	33.3	11.8	33.3
3l	40.0	43.8	23.5	17.4	27.8
3m	31.6	50.0	4.8	2.9	33.3
3n	10.5	14.3	14.0	14.7	14.8
3o	21.1	35.7	18.0	8.8	25.3
3p	31.6	35.0	19.0	20.6	48.1
3q	26.7	18.8	17.6	13.0	16.7
3r	52.4	26.7	6.7	0	13.6
2a	35.3	20.0	16.7	9.1	100.0
2g	0	12.0	0	7.0	6.2
2r	0	13.3	0	8.5	16.1
4a	11.8	33.3	22.2	9.1	25.8
4g	19.2	28.0	8.3	15.5	18.5
4r	5.9	26.7	27.8	13.6	25.0
5a	42.3	44.0	0	21.1	6.2
5g	30.8	16.0	22.2	19.5	18.5
5r	42.3	40.0	8.3	21.1	24.7
2aa	13.3	19.2	31.6	0	5.8
2ab	16.7	7.7	31.6	20.0	6.0
Anthranilamide	42.3	52.0	27.8	38.0	43.2
Fenpiclonil	100	100	18.0	100	100

The data is the average of three duplicate results.

did not increase its activity. And the methylated pyrrole ring would weaken its fungicidal activity. The **2a** could be considered as a potential compound for further structural optimization.

5. Experimental section

5.1. Materials and methods

^{1}H NMR, ^{13}C NMR, HMQC, HMBC and H–H COSY spectra were obtained at 300 MHz using a Bruker AV300 spectrometer or at 400 MHz using a Bruker AV400 spectrometer in $CDCl_3$ or DMSO-d_6 solution with tetramethylsilane (TMS) as the internal standard. Chemical shift values (δ) were given in ppm. High-resolution mass spectrometry (HRMS) data were obtained on a Varian QFT-ESI instrument. The melting points were determined on an X-4 binocular microscope melting point apparatus (Beijing Tech Instruments Co., Beijing, China) and were uncorrected. Yields were not optimized. The reagents were all analytically or chemically pure. All solvents and liquid reagents were dried by standard methods in advance and distilled before use. Pyrrole and benzyl halogen (**6d**–**q**) were purchased from the Alfa Aesar Company (Tianjin, China). **6a**–**c** [24,25], **6r** [26] and anthranilamide [10] were synthesized according to literatures. Fenpiclonil was bought from labor Dr. Ehrenstorfer-Schäfers (Augsburg, Germany).

5.2. Synthesis

5.2.1. General synthetic

*5.2.1.1. Synthesis procedures for compounds **1**–**5**.* 1*H*-Pyrrole-2-carbaldehyde **1** was synthesized referencing to the literatures [27,28]. 1*H*-Pyrrole-2-carboxylic acid **2** was synthesized through an improved procedure referencing to literature [16]: To a suspension of sliver oxide was added **1** in ethanol. After stirring for 1 h at reflux (It is failed to get compound **2** when the mixture was stirred for 10 h at room temperature according to the literature [16]), the precipitate was filtered out and washed with hot water. The combined filtrate and washings were acidified with concentrated hydrochloride acid at room temperature and extracted with ethyl acetate, drying ($MgSO_4$) and removal the ethyl acetate under vacuum to give the crude **2**. 4,5-Dibromo-1*H*-pyrrole-2-carboxylic acid **3** and 3,4,5-tribromo-1*H*-pyrrole-2-carboxylic acid **4** were synthesized referencing to the literature [7,9]. When the bromine was 3 equivalents of the **2** in HOAc and the reaction time was prolonged. Compound **2** could be fully converted to the crude product **4** which could be also obtained from compound **3** reacting with the equivalent of bromine in HOAc. The crude **4** was then recrystallized in the solution of ethanol/water to give the pure

Table 3
EC50 (μg mL^{-1}) values of **2a**, **3a** and fenpiclonil.

2a	$Y = a+bx$	EC_{50}	R	**3a**	$Y = a+bx$	EC_{50}	R
A. solani		>50		*A. solani*	$Y = 3.311 + 1.296x$	20.03	0.99
C. arachidicola		>50		*C. arachidicola*	$Y = 2.735 + 1.632x$	24.39	0.99
F. omysporum		>50		*F. omysporum*		>50	
G. zeae		>50		*G. zeae*		>50	
P. piricola	$Y = 4.283 + 1.095x$	4.50	0.94	*P. piricola*	$Y = 3.380 + 1.634x$	9.78	0.98
Fenpiclonil		$Y = a + bx$			EC_{50}		R
A. solani		$Y = 5.340 + 1.322x$			0.55		0.96
C. arachidicola		$Y = 5.477 + 1.153x$			0.38		0.95
F. omysporum					>50		
G. zeae		$Y = 4.584 + 1.780x$			1.71		0.97
P. piricola		$Y = 5.226 + 2.352x$			0.80		0.99

4. Conclusion

Twenty-nine pyrrole alkaloid analogs were designed and synthesized with a novel and facile procedure. The results of bioassay showed that the fungicidal activities of most target compounds exhibited moderate activities against *A. solan*i, *C. arachidicola*, *F. omysporum*, *G. zeae* and *P. piricola* at the dosage of 50 μg mL^{-1}. The possible SAR of those target compounds were as follows: H-10 and H-11 substituted by $-OCH_3$; or H-10 and H-11 substituted by $-OCH_3$ and propargyl; H-11 substituted by –F or –CN; H-12 substituted by –Cl; H-13 substituted by –F in the aroma ring might improve their fungicidal activities. The addition of bromine atoms to the pyrrole ring 2 and 3 position might enhance its antifungal activity and spectrum. The above terms were essential for high fungicidal activity in this type of pyrrole alkaloid analogs. The addition of chlorine atoms at 2 and 3 position or three bromine atoms to the pyrrole ring

product. 4,5-Dichloro-1*H*-pyrrole-2-carboxylic acid **5** was synthesized through an improved procedure referencing to literature [17]: To pyrrole-2-carboxylic acid **2** in the mixture solution of dichloromethane and acetone (v/v = 4:1, It is failed to get compound **5** when the solution was only dichloromethane and stirred for 6 h at room temperature according to the literature [17]), sulfuryl chloride was added dropwise in dichloromethane. The reaction continued for 0.5 h at room temperature; then the reaction mixture was poured slowly into water, followed by extraction with ethyl acetate and washed with water, evaporation the solvent to give the crude product **5** (Scheme 1).

*5.2.1.1.1. 1H-Pyrrole-2-carbaldehyde (**1**).* Light yellow solid; yield 58.8%; mp 40–42 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.97 (brs, 1H, Pyrrole–NH), 9.49 (s, 1H, –CHO), 7.18 (brs, 1H, Pyrrole–H), 7.01 (brs, 1H, Pyrrole–H), 6.33 (brs, 1H, Pyrrole–H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 179.6, 132.8, 127.4, 122.3, 111.3.

*5.2.1.1.2. 1H-Pyrrole-2-carboxylic acid (**2**).* White solid; yield 67.9%; mp 193–195 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.24 (brs, 1H, –COOH), 11.72 (brs, 1H, Pyrrole–NH), 6.95 (brs, 1H, Pyrrole–H), 6.72 (brs, 1H, Pyrrole–H), 6.13 (brs, 1H, Pyrrole–H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 161.8, 123.3, 122.8, 114.6, 109.2.

*5.2.1.1.3. 4,5-Dibromo-1H-pyrrole-2-carboxylic acid (**3**).* Light red solid; yield 67.2%; mp 180–182 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.96 (brs, 1H, –COOH), 6.83 (brs, 1H, Pyrrole–H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 160.2, 124.9, 116.8, 106.6, 98.7.

*5.2.1.1.4. 3,4,5-Tribromo-1H-pyrrole-2-carboxylic acid (**4**).* Red solid; yield 50.1%; mp 202–204 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 13.36 (brs, 1H, –COOH), 13.16 (brs, 1H, Pyrrole–NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 159.3, 122.5, 106.6, 104.2, 103.3.

*5.2.1.1.5. 4,5-Dichloro-1H-pyrrole-2-carboxylic acid (**5**).* Purple solid; yield 75.0%; mp 169–171 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 13.02 (brs, 1H, –COOH), 12.84 (brs, 1H, Pyrrole–NH), 6.81 (brs, 1H, Pyrrole–H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 160.3, 121.6, 116.6, 113.9, 108.8.

*5.2.1.2. Synthetic procedures for compounds **7a**–**r**.* Compound **7a** was synthesized referencing to the literatures [18,29]. To be pointed out, the crude products of **7b**, **7i**, **7k**, **7l**, **7n**–**p** required to wash with the solution of ethyl acetate/petroleum ether (v/v = 1:5) again; In the preparation of **7r**, the whole mixture of *N*-hydroxyphthalimide, sodium hydroxide and **6r** in DMF needed to be stirred at 80 °C for 2 h, cooled, then poured into water, and stirred for 1 h to afford a mucilaginous solid which was collected by vacuum filtration and washed with water. The above mucilaginous solid was then dissolved in the solution of dichloromethane/water (v/v = 1:1), leaving the organic layer and removal the solvent under vacuum to give the crude **7r** which was then recrystallized in the solution of ethyl acetate/petroleum ether (v/v = 1:4). All the substituents at the benzene ring were listed in Scheme 2 and Table 1.

*5.2.1.2.1. 2-(3-Methoxy-4-prop-2-ynyloxy-benzyloxy)-isoindole-1,3-dione (**7a**).* White solid; yield 79.8%; mp 151–153 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.80 (brd, J = 2.4 Hz, 2H, Ar–H), 7.73 (brs, 2H, Ar–H), 7.17 (s, 1H, Ar–H), 6.99–7.01 (m, 2H, Ar–H), 5.17 (s, 2H, Ar–CH_2O–), 4.75 (s, 2H, Ar–OCH_2–), 3.91 (s, 3H, Ar–OCH_3), 2.50 (s, 1H, alkynyl-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.5 (2C), 149.5, 147.5, 134.4 (2C), 128.8 (2C), 127.5, 123.4 (2C), 122.3, 113.5, 113.2, 79.6, 78.2, 75.9, 56.6, 55.9.

*5.2.1.2.2. 2-(3,4-Dimethoxy-benzyloxy)-isoindole-1,3-dione (**7b**).* White solid; yield 49.3%; mp 143–145 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.80 (dt, J = 8.0, 3.2 Hz, 2H, Ar–H), 7.73 (dt, J = 8.0, 3.2 Hz, 2H, Ar–H), 7.13 (s, 1H, Ar–H), 7.03 (d, J = 8.0 Hz, 1H, Ar–H), 6.82 (d, J = 8.0 Hz, 1H, Ar–H), 5.17 (s, 2H, Ar–CH_2O–), 3.91 (s, 3H, Ar–OCH_3), 3.87 (s, 3H, Ar–OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.5 (2C), 149.8, 148.9, 134.4 (2C), 128.8 (2C), 126.1, 123.4 (2C), 122.7, 112.7, 110.6, 79.7, 55.9, 55.8.

*5.2.1.2.3. 2-(Benzo[1,3]dioxol-5-ylmethoxy)-isoindole-1,3-dione (**7c**).* White solid; yield 83.3%; mp 172–174 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.80 (dt, J = 8.0, 3.2 Hz, 2H, Ar–H), 7.73 (dt, J = 8.0, 3.2 Hz, 2H, Ar–H), 7.06 (s, 1H, Ar–H), 6.95 (d, J = 8.0 Hz, 1H, Ar–H), 6.77 (d, J = 8.0 Hz, 1H, Ar–H), 5.97 (s, 2H, –OCH_2O–), 5.10 (s, 2H, Ar–CH_2O–). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.5 (2C), 148.5, 147.8, 134.4 (2C), 128.8 (2C), 127.4, 124.1, 123.5 (2C), 110.3, 108.1, 101.2, 79.7.

*5.2.1.2.4. 2-Benzyloxy-isoindole-1,3-dione (**7d**).* White solid; yield 67.5%; mp 141–143 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.79 (dt, J = 8.8, 3.2 Hz, 2H, Ar–H), 7.71 (dt, J = 8.8, 3.2 Hz, 2H, Ar–H), 7.51–7.54 (m, 2H, Ar–H), 7.36–7.37 (m, 3H, Ar–H), 5.20 (s, 2H, Ar–CH_2O–). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.5 (2C), 134.4 (2C), 133.6, 129.9 (2C), 129.3, 128.8 (2C), 128.5 (2C), 123.5 (2C), 79.8.

*5.2.1.2.5. 2-(2-Fluoro-benzyloxy)-isoindole-1,3-dione (**7e**).* White solid; yield 79.2%; mp 153–155 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.80 (dt, J = 8.4, 3.2 Hz, 2H, Ar–H), 7.73 (dt, J = 8.4, 3.2 Hz, 2H, Ar–H), 7.53–7.57 (m, 1H, Ar–H), 7.34–7.37 (m, 1H, Ar–H), 7.14–7.18 (m, 1H, Ar–H), 7.05–7.09 (m, 1H, Ar–H), 5.29 (s, 2H, Ar–CH_2O–). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.3 (2C), 162.8 (Ar–F), 160.3 (Ar–F), 134.4 (2C), 132.2, 131.5, 128.8 (2C), 124.3, 123.5 (2C), 121.2, 115.5, 73.0.

*5.2.1.2.6. 2-(3-Fluoro-benzyloxy)-isoindole-1,3-dione (**7f**).* White solid; yield 54.8%; mp 129–131 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.74 (dt, J = 8.4, 3.2 Hz, 2H, Ar–H), 7.67 (dt, J = 8.4, 3.2 Hz, 2H, Ar–H), 7.24–7.28 (m, 1H, Ar–H), 7.18–7.24 (m, 2H, Ar–H), 6.98–7.01 (m, 1H, Ar–H), 5.12 (s, 2H, Ar–CH_2O–). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.9 (Ar–F), 161.4 (Ar–F), 163.4 (2C), 136.0, 134.5 (2C), 130.1, 128.8 (2C), 125.2, 123.6 (2C), 116.5, 116.2, 78.9.

*5.2.1.2.7. 2-(4-Fluoro-benzyloxy)-isoindole-1,3-dione (**7g**).* White solid; yield 43.7%; mp 148–150 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.81 (dt, J = 8.4, 3.2 Hz, 2H, Ar–H), 7.74 (dt, J = 8.4, 3.2 Hz, 2H, Ar–H), 7.50–7.54 (m, 2H, Ar–H), 7.04–7.08 (m, 2H, Ar–H), 5.17 (s, 2H, Ar–CH_2O–). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.6 (Ar–F), 162.1 (Ar–F), 163.4 (2C), 134.5 (2C), 131.9 (2C), 129.6, 128.8 (2C), 123.5 (2C), 115.6 (2C), 79.0.

*5.2.1.2.8. 2-(2-Chloro-benzyloxy)-isoindole-1,3-dione (**7h**).* White solid; yield 29.0%; mp 154–156 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.81 (dt, J = 8.4, 3.2 Hz, 2H, Ar–H), 7.74 (dt, J = 8.4, 3.2 Hz, 2H, Ar–H), 7.62–7.64 (m, 1H, Ar–H), 7.37–7.39 (m, 1H, Ar–H), 7.29–7.31 (m, 2H, Ar–H), 5.36 (s, 2H, Ar–CH_2O–). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.3 (2C), 134.7, 134.4 (2C), 131.9, 131.7, 130.5, 129.6, 128.8 (2C), 127.0, 123.5 (2C), 76.4.

*5.2.1.2.9. 2-(3-Chloro-benzyloxy)-isoindole-1,3-dione (**7i**).* White solid; yield 29.2%; mp 134–136 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.82 (dt, J = 8.4, 3.2 Hz, 2H, Ar–H), 7.75 (dt, J = 8.4, 3.2 Hz, 2H, Ar–H), 7.54 (s, 1H, Ar–H), 7.43–7.44 (m, 1H, Ar–H), 7.32–7.34 (m, 2H, Ar–H), 5.17 (s, 2H, Ar–CH_2O–). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.4 (2C), 135.6, 134.5 (2C), 134.3, 129.8, 129.7, 129.4, 128.8 (2C), 127.7, 123.6 (2C), 78.9.

*5.2.1.2.10. 2-(6-Chloro-pyridin-3-ylmethoxy)-isoindole-1,3-dione (**7j**).* White solid; yield 67.4%; mp 151–153 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.54 (s, 1H, Pyridine-H), 8.05 (d, J = 8.0 Hz, 1H, Pyridine-H), 7.86 (brs, 4H, Ar–H), 7.58 (d, J = 8.0 Hz, 1H, Pyridine-H), 5.24 (s, 2H, Pyridine–CH_2O–). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 163.0 (2C), 150.8 (2C), 141.1, 134.8 (2C), 129.9, 128.4 (2C), 124.1, 123.3 (2C), 75.6.

*5.2.1.2.11. 2-(2,4-Dichloro-benzyloxy)-isoindole-1,3-dione (**7k**).* White solid; yield 51.8%; mp 154–156 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.82 (dt, J = 8.4, 3.2 Hz, 2H, Ar–H), 7.75 (dt, J = 8.4, 3.2 Hz, 2H, Ar–H), 7.59 (d, J = 8.4 Hz, 1H, Ar–H), 7.41 (d, J = 1.6 Hz, 1H, Ar–H), 7.27 (dt, J = 8.4, 1.6 Hz, 1H, Ar–H), 5.32 (s, 2H, Ar–CH_2O–). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.3 (2C), 135.8, 135.3, 134.5 (2C), 132.4, 130.5, 129.5, 128.7 (2C), 127.4, 123.6 (2C), 75.7.

*5.2.1.2.12. 2-(3,4-Dichloro-benzyloxy)-isoindole-1,3-dione (**7l**).* Purple solid; yield 51.0%; mp 182–184 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.82 (dt, J = 8.4, 3.2 Hz, 2H, Ar–H), 7.75 (dt, J = 8.4, 3.2 Hz,

2H, Ar–H), 7.64 (d, J = 1.6 Hz, 1H, Ar–H), 7.46 (d, J = 8.4 Hz, 1H, Ar–H), 7.39 (dt, J = 8.4, 1.6 Hz, 1H, Ar–H), 5.15 (s, 2H, Ar–CH_2O–). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.4 (2C), 134.6 (2C), 133.9, 133.5, 132.7, 131.4, 130.6, 128.8 (2C), 128.7, 123.6 (2C), 78.2.

*5.2.1.2.13. 2-(4-Bromo-benzyloxy)-isoindole-1,3-dione (**7m**).* White solid; yield 60.6%; mp 143–145 °C; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.81 (dt, J = 8.0, 3.2 Hz, 2H, Ar–H), 7.74 (dt, J = 8.0, 3.2 Hz, 2H, Ar–H), 7.50 (d, J = 8.4 Hz, 2H, Ar–H), 7.41 (d, J = 8.4 Hz, 2H, Ar–H), 5.16 (s, 2H, Ar–CH_2O–). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.4 (2C), 134.5 (2C), 132.7, 131.7 (2C), 131.4 (3C), 128.7 (2C), 123.6 (2C), 78.9.

*5.2.1.2.14. 2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yloxymethyl)-benzonitrile (**7n**).* Purple solid; yield 54.3%; mp 195–197 °C; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.28–7.81 (m, 8H, Ar–H), 5.42 (s, 2H, Ar–CH_2O–). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 163.2 (2C), 137.3, 134.6 (2C), 133.0, 132.9, 130.8, 129.6, 128.7 (2C), 123.6 (2C), 116.8, 113.0, 77.3.

*5.2.1.2.15. 3-(1,3-Dioxo-1,3-dihydro-isoindol-2-yloxymethyl)-benzonitrile (**7o**).* White solid; yield 54.5%; mp 173–175 °C; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.79–7.84 (m, 4H, Ar–H), 7.75–7.78 (m, 2H, Ar–H), 7.60–7.66 (m, 1H, Ar–H), 7.50–7.55 (m, 1H, Ar–H), 5.23 (s, 2H, Ar–CH_2O–). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 163.3 (2C), 135.4, 134.6 (2C), 133.8, 132.9, 132.8, 129.4, 128.7 (2C), 123.6 (2C), 118.2, 112.8, 78.4.

*5.2.1.2.16. 4-(1,3-Dioxo-1,3-dihydro-isoindol-2-yloxymethyl)-benzonitrile (**7p**).* White solid; yield 54.0%; mp 194–196 °C; ^1H NMR (400 MHz, DMSO-d_6) δ: 7.89 (d, J = 8.4 Hz, 2H, Ar–H), 7.86 (brs, 4H, Ar–H), 7.74 (d, J = 8.4 Hz, 2H, Ar–H), 5.28 (s, 2H, Ar–CH_2O–). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 163.0 (2C), 139.8, 134.8 (2C), 132.3 (2C), 130.0 (2C), 128.4 (2C), 123.2 (2C), 118.5, 111.5, 78.1.

*5.2.1.2.17. 2-(4-Nitro-benzyloxy)-isoindole-1,3-dione (**7q**).* White solid; yield 61.7%; mp 191–193 °C; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.25 (d, J = 8.0 Hz, 2H, Ar–H), 7.80 (d, J = 8.0 Hz, 2H, Ar–H), 7.74 (brs, 4H, Ar–H), 5.31 (s, 2H, Ar–CH_2O–). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.3 (2C), 148.3, 140.8, 134.7 (2C), 130.0 (2C), 128.6 (2C), 123.7 (4C), 78.3.

*5.2.1.2.18. 2-[2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yloxymethyl)-phenyl]-3-methoxy-acrylic acid methyl ester (**7r**).* Gray solid; yield 32.6%; mp 162–164 °C; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.79 (brs, 3H, Ar–H), 7.71 (brs, 2H, Ar–H), 7.62 (s, 1H, =$CHOCH_3$), 7.38 (brs, 2H, Ar–H), 7.15 (brs, 1H, Ar–H), 5.12 (s, 2H, Ar–CH_2O–), 3.75 (s, 3H, –OCH_3), 3.61 (s, 2H, –OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.8, 163.3 (2C), 160.6, 134.3 (2C), 133.1, 133.0, 130.9, 130.5, 129.0, 128.9 (2C), 128.0, 123.3 (2C), 109.5, 77.3, 61.9, 51.6.

*5.2.1.3. Synthetic procedures for compounds **8a**–**r**.* Compound **8a** was synthesized by a facile method improving on the literature [18]: To a solution of compound **7a** in anhydrous ethanol, hydrazine monohydrate was added. The mixture was refluxed for 1 h. The resulting solid was removed by filtration, and the filtrate was evaporated on a rotavap. The residue was slurried in anhydrous ether and filtered, and the filtrate was washed with water again. The ether layer was separated, dried with $CaCl_2$ and evaporated to afford Compound **8a**. According to the above process, Compounds **8b**–**q** were prepared from **7b**–**q** respectively. To be pointed out, as the product **8r** was unstable, the mixture of **7r**, ethanol and hydrazine monohydrate was stirred overnight at room temperature. The final ether layer was dried with $CaCl_2$ and used rapidly in the next step of synthesis. All the substituents at the benzene ring were listed in Scheme 2 and Table 1. As substance **8b**–**q** was unstable, the boiling points of them were not detected.

*5.2.1.3.1. O-(3-Methoxy-4-prop-2-ynyloxy-benzyl)-hydroxylamine (**8a**).* White solid; yield 68.9%; mp 30–32 °C; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.00 (d, J = 8.0 Hz, 1H, Ar–H), 6.93 (s, 1H, Ar–H), 6.90 (d, J = 8.0 Hz, 1H, Ar–H), 5.38 (s, 2H, $-NH_2$), 4.75 (d, J = 2.0 Hz, 2H, Ar–OCH_2–), 4.62 (s, 2H, Ar–CH_2O–), 3.88 (s, 3H, Ar–OCH_3), 2.50 (s, 1H, alkynyl-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 149.7, 146.6, 131.4, 120.8, 114.1, 112.0, 78.5, 77.8, 75.8, 56.7, 55.8.

*5.2.1.3.2. O-(3,4-Dimethoxy-benzyl)-hydroxylamine (**8b**).* Colorless oil; yield 20.5%; ^1H NMR (400 MHz, $CDCl_3$) δ: 6.89–6.91 (m, 2H, Ar–H), 6.82–6.85 (m, 1H, Ar–H), 4.61 (s, 2H, Ar–CH_2O–), 3.88 (s, 3H, Ar–OCH_3), 3.86 (s, 3H, Ar–OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 149.0, 148.9, 129.9, 121.0, 111.6, 110.0, 77.8, 55.8 (2C).

*5.2.1.3.3. O-Benzo[1,3]dioxol-5-ylmethyl-hydroxylamine (**8c**).* Colorless oil; yield 69.6%; ^1H NMR (400 MHz, $CDCl_3$) δ: 6.82 (s, 1H, Ar–H), 6.73–6.75 (m, 2H, Ar–H), 5.86 (s, 2H, –OCH_2O–), 5.32 (brs, 2H, $-NH_2$), 4.51 (s, 2H, Ar–CH_2O–). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 147.7, 147.3, 131.4, 122.0, 108.9, 108.0, 101.0, 77.5.

*5.2.1.3.4. O-Benzylhydroxylamine (**8d**).* Colorless oil; yield 58.8%; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.29–7.31 (m, 5H, Ar–H), 5.25 (brs, 2H, $-NH_2$), 4.61 (s, 2H, Ar–CH_2O–). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 137.6, 128.5 (2C), 128.4 (2C), 127.9, 77.9.

*5.2.1.3.5. O-(2-Fluoro-benzyl)-hydroxylamine (**8e**).* Colorless oil; yield 49.3%; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.36–7.41 (m, 1H, Ar–H), 7.26–7.28 (m, 1H, Ar–H), 7.01–7.14 (m, 2H, Ar–H), 5.42 (brs, 2H, $-NH_2$), 4.74 (s, 2H, Ar–CH_2O–). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.8 (Ar–F), 159.5 (Ar–F), 130.8, 129.7, 124.5, 123.9, 115.4, 71.3.

*5.2.1.3.6. O-(3-Fluoro-benzyl)-hydroxylamine (**8f**).* Colorless oil; yield 44.1%; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.26–7.31 (m, 1H, Ar–H), 7.04–7.10 (m, 2H, Ar–H), 6.95–6.99 (m, 1H, Ar–H), 5.45 (brs, 2H, $-NH_2$), 4.63 (s, 2H, Ar–CH_2O–). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.1 (Ar–F), 161.6 (Ar–F), 140.3, 130.0, 123.7, 115.0, 114.7, 76.9.

*5.2.1.3.7. O-(4-Fluoro-benzyl)-hydroxylamine (**8g**).* Colorless oil; yield 66.7%; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.29–7.32 (m, 2H, Ar–H), 7.00–7.04 (m, 2H, Ar–H), 5.38 (brs, 2H, $-NH_2$), 4.61 (s, 2H, Ar–CH_2O–). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.7 (Ar–F), 161.3 (Ar–F), 133.3, 130.2 (2C), 115.3 (2C), 77.1.

*5.2.1.3.8. O-(2-Chloro-benzyl)-hydroxylamine (**8h**).* Colorless oil; yield 90.9%; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.38–7.40 (m, 1H, Ar–H), 7.31–7.33 (m, 1H, Ar–H), 7.17–7.21 (m, 2H, Ar–H), 5.26 (brs, 2H, $-NH_2$), 4.76 (s, 2H, Ar–CH_2O–). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 135.2, 133.6, 129.9, 129.4, 129.0, 126.7, 74.9.

*5.2.1.3.9. O-(3-Chloro-benzyl)-hydroxylamine (**8i**).* Colorless oil; yield 88.0%; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.34 (s, 1H, Ar–H), 7.25–7.26 (m, 2H, Ar–H), 7.20–7.21 (m, 1H, Ar–H), 5.43 (brs, 2H, $-NH_2$), 4.62 (s, 2H, Ar–CH_2O–). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 139.8, 134.3, 129.7, 128.2, 128.0, 126.2, 76.9.

*5.2.1.3.10. O-(6-Chloro-pyridin-3-ylmethyl)-hydroxylamine (**8j**).* White solid; yield 57.8%; mp 58–60 °C; ^1H NMR (400 MHz, DMSO-d_6) δ: 8.34 (d, J = 2.1 Hz, 1H, Pyridine-H), 7.68 (dt, J = 8.1, 2.1 Hz, 1H, Pyridine-H), 7.30 (d, J = 8.1 Hz, 1H, Pyridine-H), 5.60 (brs, 2H, $-NH_2$), 4.65 (s, 2H, Pyridine-CH_2O–). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 150.6, 149.5, 138.9, 132.2, 123.9, 74.0.

*5.2.1.3.11. O-(2,4-Dichloro-benzyl)-hydroxylamine (**8k**).* Colorless oil; yield 90.3%; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.34 (s, 1H, Ar–H), 7.32 (d, J = 8.0 Hz, 1H, Ar–H), 7.20 (d, J = 8.0 Hz, 1H, Ar–H), 5.50 (brs, 2H, $-NH_2$), 4.72 (s, 2H, Ar–CH_2O–). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 134.2, 134.0 (2C), 130.6, 129.2, 126.9, 74.2.

*5.2.1.3.12. O-(3,4-Dichloro-benzyl)-hydroxylamine (**8l**).* Colorless oil; yield 94.3%; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.40 (s, 1H, Ar–H), 7.36 (d, J = 8.0 Hz, 1H, Ar–H), 7.13 (d, J = 8.0 Hz, 1H, Ar–H), 5.45 (brs, 2H, $-NH_2$), 4.57 (s, 2H, Ar–CH_2O–). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 138.1, 132.3, 131.6, 130.3, 130.0, 127.4, 76.1.

*5.2.1.3.13. O-(4-Bromo-benzyl)-hydroxylamine (**8m**).* Colorless oil; yield 94.0%; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.44 (d, J = 8.1 Hz, 2H, Ar–H), 7.19 (d, J = 8.1 Hz, 2H, Ar–H), 5.39 (brs, 2H, $-NH_2$), 4.58 (s, 2H, Ar–CH_2O–). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 136.6, 131.5 (2C), 130.0 (2C), 121.8, 77.0.

*5.2.1.3.14. 2-Aminooxymethyl-benzonitrile (**8n**).* Colorless oil; yield 70.2%; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.52–7.57 (m, 1H, Ar–H), 7.43–7.51 (m, 2H, Ar–H), 7.31–7.34 (m, 1H, Ar–H), 5.50 (brs, 2H, $-NH_2$), 4.76 (s, 2H, Ar–CH_2O–). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 141.2, 132.8, 132.7, 129.4, 128.3, 117.4, 112.2, 75.2.

*5.2.1.3.15. 3-Aminooxymethyl-benzonitrile (**8o**).* Colorless oil; yield 80.2%; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.63 (s, 1H, Ar–H), 7.56–7.58 (m, 2H, Ar–H), 7.43–7.47 (m, 1H, Ar–H), 5.57 (brs, 2H, $-NH_2$), 4.69 (s, 2H, Ar–CH_2O–).^{13}C NMR (75 MHz, $CDCl_3$) δ: 139.5, 132.4, 131.4, 131.2, 129.1, 118.7, 112.1, 76.2.

*5.2.1.3.16. 4-Aminooxymethyl-benzonitrile (**8p**).* Colorless oil; yield 81.7%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.50 (d, J = 6.8 Hz, 2H, Ar–H), 7.35 (d, J = 6.8 Hz, 2H, Ar–H), 5.48 (brs, 2H, $-NH_2$), 4.61 (s, 2H, Ar–CH_2O–). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 143.5, 132.1 (2C), 128.4 (2C), 118.8, 111.2, 76.5.

*5.2.1.3.17. O-(4-Nitro-benzyl)-hydroxylamine (**8q**).* Colorless oil; yield 86.5%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.14 (d, J = 8.4 Hz, 2H, Ar–H), 7.50 (d, J = 8.4 Hz, 2H, Ar–H), 5.70 (brs, 2H, $-NH_2$), 4.77 (s, 2H, Ar–CH_2O–). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 147.2, 145.7, 128.3 (2C), 123.4 (2C), 76.2.

*5.2.1.4. Synthetic procedures for target compounds **3a**–**r**, **2a**, **2g**, **2r**, **4a**, **4g**, **4r**, **5a**, **5g**, **5r**.* Compound **3a** was synthesized as follows: To a solution of compound **3** (0.40 g, 1.5 mmol) in dry CH_2Cl_2 (15.0 mL) 0.5 mL oxalyl choride was added and stirred. 10 min later, two drops of dry DMF was added to the above solution. The mixture was stirred overnight at room temperature. Then the dark solution was evaporated under vacuum to get the 4,5-dibromo-1*H*-pyrrole-2-carbonyl chloride. Compounds **8a** (0.31 g, 1.5 mmol) was dissolved in the solution of dry CH_2Cl_2 (20.0 mL) and anhydrous pyridine (0.3 mL). The 4,5-dibromo-1*H*-pyrrole-2-carbonyl chloride diluted in dry CH_2Cl_2 (10.0 mL) was added dropwise to the above solution of **8a**. The whole mixture continued to stir for 1 h at room temperature after the carbonyl chloride dripped off, then 50.0 mL water and 100.0 mL ethyl acetate were added, washed with 2 N dilute hydrochloric acid, saturated sodium bicarbonate and water respectively. Separating the organic layer, the solvent was removed by distillation. The residue was recrystallized with ethyl acetate/petroleum ether (60–90 °C, v/v = 1:4) to give 4, 5-dibromo-*N*-(3-methoxy-4-(prop-2-ynyloxy) benzyloxy)-1*H*-pyrrole-2-carboxamide (**3a**, 0.38 g, 56.5%). Using the same procedure, compounds **2a**–**5r** were prepared from **8a**–**r** with corresponding carbonyl chloride respectively. To be pointed out, compound **3r** need to be isolated from its crude residue by flash chromatography on silica gel eluting with ethyl acetate/petroleum [elution solvent: ethyl acetate/petroleum ether (60–90 °C), v/v = 1:4]. All the substituents at the benzene ring were listed in Scheme 2 and Table 1.

*5.2.1.4.1. 4,5-Dibromo-1H-pyrrole-2-carboxylic acid (3-methoxy-4-prop-2-ynyloxy-benzyloxy)-amide (**3a**).* Gray solid; yield 56.5%; mp 164–166 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.84 (s, 1H, Pyrrole–NH), 11.40 (brs, 1H, –CONH–), 7.08 (s, 1H, Ar–H), 7.02 (d, J = 8.0 Hz, 1H, Ar–H), 6.93 (d, J = 8.0 Hz, 1H, Ar–H), 6.80 (d, J = 2.0 Hz, 1H, Pyrrole–H), 4.82 (s, 2H, Ar–CH_2O–), 4.78 (d, J = 2.0 Hz, 2H, Ar–OCH_2–), 3.78 (s, 3H, Ar–OCH_3), 3.54 (s, 1H, alkynyl-H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 157.6, 148.9, 146.5, 129.3, 125.2, 121.2, 113.6, 112.9 (2C), 105.4, 97.9, 79.2, 78.2, 77.2, 55.9, 55.4. HRMS, m/z 456.9223. Calcd for $C_{16}H_{14}Br_2N_2O_4$, 456.9227.

*5.2.1.4.2. 4,5-Dibromo-1H-pyrrole-2-carboxylic acid (3,4-dimethoxy-benzyloxy)-amide (**3b**).* Gray solid; yield 30.1%; mp 197–199 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.83 (s, 1H, Pyrrole–NH), 11.38 (brs, 1H, –CONH–), 7.03 (s, 1H, Ar–H), 6.93 (brs, 2H, Ar–H), 6.79 (s, 1H, Pyrrole–H), 4.80 (s, 2H, Ar–CH_2O–), 3.76 (s, 3H, Ar–OCH_3), 3.75 (s, 3H, Ar–OCH_3). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 157.6, 148.9, 148.5, 128.1, 125.3, 121.6, 112.7 (2C), 111.3, 105.4, 97.8, 77.3, 55.4, 55.3. HRMS, m/z 432.9219. Calcd for $C_{14}H_{14}Br_2N_2O_4$, 432.9227.

*5.2.1.4.3. 4,5-Dibromo-1H-pyrrole-2-carboxylic acid (benzo[1,3] dioxol-5-ylmethoxy)-amide (**3c**).* Gray solid; yield 61.8%; mp 99–101 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.83 (s, 1H, Pyrrole–NH), 11.39 (brs, 1H, –CONH–), 7.00 (s, 1H, Ar–H), 6.89–6.90 (m, 2H, Ar–H), 6.79 (d, J = 1.8 Hz, 1H, Pyrrole–H), 6.02 (s, 2H, $-OCH_2O$–), 4.77 (s, 2H, Ar–CH_2O–). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 157.6, 147.2, 147.1, 129.6, 125.2, 122.8, 112.7, 109.3, 107.9, 105.4, 101.0, 97.8, 77.1. HRMS, m/z 416.8906. Calcd for $C_{13}H_{10}Br_2N_2O_4$, 416.8914.

*5.2.1.4.4. 4,5-Dibromo-1H-pyrrole-2-carboxylic acid benzyloxy-amide (**3d**).* Gray solid; yield 34.0%; mp 113–115 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.94 (s, 1H, Pyrrole–NH), 9.56 (brs, 1H, –CONH–), 7.13–7.21 (m, 5H, Ar–H), 6.67 (s, 1H, Pyrrole–H), 4.82 (s, 2H, Ar–CH_2O–). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.9, 134.5, 129.3 (2C), 129.0, 128.7 (2C), 123.7, 115.3, 107.3, 100.2, 79.1. HRMS, m/z 372.9022. Calcd for $C_{12}H_{10}Br_2N_2O_2$, 372.9016.

*5.2.1.4.5. 4,5-Dibromo-1H-pyrrole-2-carboxylic acid (2-fluorobenzyloxy)-amide (**3e**).* Gray solid; yield 57.6%; mp 82–84 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.86 (s, 1H, Pyrrole–NH), 11.47 (brs, 1H, –CONH–), 7.43–7.50 (m, 2H, Ar–H), 7.21–7.23 (m, 2H, Ar–H), 6.79 (s, 1H, Pyrrole–H), 4.95 (s, 2H, Ar–CH_2O–). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 162.0 (Ar–F), 159.6 (Ar–F), 157.7, 132.1, 130.8, 125.1, 124.3, 122.6, 115.3, 112.8, 105.5, 97.9, 70.7. HRMS, m/z 390.8922. Calcd for $C_{12}H_9Br_2FN_2O_2$, 390.8922.

*5.2.1.4.6. 4,5-Dibromo-1H-pyrrole-2-carboxylic acid (3-fluorobenzyloxy)-amide (**3f**).* Gray solid; yield 63.8%; mp 99–101 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.87 (s, 1H, Pyrrole–NH), 11.50 (brs, 1H, –CONH–), 7.42–7.44 (m, 1H, Ar–H), 7.28–7.30 (m, 2H, Ar–H), 7.19–7.26 (m, 1H, Ar–H), 6.79 (s, 1H, Pyrrole–H), 4.91 (s, 2H, Ar–CH_2O–). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 163.3 (Ar–F), 160.8 (Ar–F), 157.8, 138.8, 130.3, 125.1, 124.6, 115.3, 114.9, 112.9, 105.7, 97.9, 76.5. HRMS, m/z 390.8925. Calcd for $C_{12}H_9Br_2FN_2O_2$, 390.8922.

*5.2.1.4.7. 4,5-Dibromo-1H-pyrrole-2-carboxylic acid (4-fluorobenzyloxy)-amide (**3g**).* Gray solid; yield 58.3%; mp 140–142 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.85 (s, 1H, Pyrrole–NH), 11.44 (brs, 1H, –CONH–), 7.47–7.50 (m, 2H, Ar–H), 7.19–7.24 (m, 2H, Ar–H), 6.80 (s, 1H, Pyrrole–H), 4.87 (s, 2H, Ar–CH_2O–). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 163.2 (Ar–F), 160.8 (Ar–F), 157.6, 132.1, 131.2 (2C), 125.1, 115.1 (2C), 112.7, 105.5, 97.9, 76.5. HRMS, m/z 390.8923. Calcd for $C_{12}H_9Br_2FN_2O_2$, 390.8922.

*5.2.1.4.8. 4,5-Dibromo-1H-pyrrole-2-carboxylic acid (2-chlorobenzyloxy)-amide (**3h**).* Gray solid; yield 44.5%; mp 124–126 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.90 (s, 1H, Pyrrole–NH), 11.54 (brs, 1H, –CONH–), 7.59–7.60 (m, 1H, Ar–H), 7.50–7.52 (m, 1H, Ar–H), 7.40–7.42 (m, 2H, Ar–H), 6.84 (s, 1H, Pyrrole–H), 5.05 (s, 2H, Ar–CH_2O–). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 157.8, 133.3, 133.2, 131.3, 130.2, 129.2, 127.2, 125.0, 112.9, 105.6, 97.9, 74.1. HRMS, m/z 406.8619. Calcd for $C_{12}H_9Br_2ClN_2O_2$, 406.8625.

*5.2.1.4.9. 4,5-Dibromo-1H-pyrrole-2-carboxylic acid (3-chlorobenzyloxy)-amide (**3i**).* Gray solid; yield 80.0%; mp 121–123 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.87 (s, 1H, Pyrrole–NH), 9.79 (brs, 1H, –CONH–), 7.21 (s, 1H, Ar–H), 7.08–7.13 (m, 3H, Ar–H), 6.69 (s, 1H, Pyrrole–H), 4.79 (s, 2H, Ar–CH_2O–). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.9, 136.7, 134.4, 129.9, 129.0 (2C), 127.1, 123.5, 115.5, 107.4, 100.3, 78.1. HRMS, m/z 406.8625. Calcd for $C_{12}H_9Br_2ClN_2O_2$, 406.8625.

*5.2.1.4.10. 4,5-Dibromo-1H-pyrrole-2-carboxylic acid (6-chloropyridin-3-ylmethoxy)-amide (**3j**).* Gray solid; yield 58.8%; mp 214–216 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.87 (s, 1H, Pyrrole–NH), 11.47 (brs, 1H, –CONH–), 8.47 (s, 1H, Pyridine-H), 7.93 (d, J = 8.0 Hz, 1H, Pyridine-H), 7.56 (d, J = 8.0 Hz, 1H, Pyridine-H), 6.78 (s, 1H, Pyrrole–H), 4.93 (s, 2H, Pyridine–CH_2O–). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 157.8, 150.1 (2C), 140.4, 131.1, 124.9, 124.0, 112.9, 105.6, 97.9, 73.8. HRMS, m/z 407.8578. Calcd for $C_{11}H_8Br_2ClN_3O_2$, 407.8578.

*5.2.1.4.11. 4,5-Dibromo-1H-pyrrole-2-carboxylic acid (2,4-dichloro-benzyloxy)-amide (**3k**).* Gray solid; yield 50.0%; mp 202–204 °C; ^{1}H NMR (400 MHz, DMSO-d_{63}) δ: 12.86 (s, 1H, Pyrrole–NH), 11.47 (s, 1H, –CONH–), 7.66 (s, 1H, Ar–H), 7.58 (d, J = 8.4 Hz, 1H, Ar–H), 7.47 (d, J = 8.4 Hz, 1H, Ar–H), 6.79 (s, 1H, Pyrrole–H), 4.98 (s, 2H, Ar–CH_2O–). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 157.8, 134.3, 133.9, 132.7, 132.6, 128.7, 127.3, 125.0, 112.9, 105.6, 97.9, 73.5. HRMS, m/z 440.8227. Calcd for $C_{12}H_8Br_2Cl_2N_2O_2$, 440.8234.

*5.2.1.4.12. 4,5-Dibromo-1H-pyrrole-2-carboxylic acid (3,4-dichloro-benzyloxy)-amide (**3l**).* Gray solid; yield 54.5%; mp 94–96 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.87 (s, 1H, Pyrrole–NH), 11.48 (brs, 1H, –CONH–), 7.74 (s, 1H, Ar–H), 7.65 (d, J = 8.0 Hz, 1H, Ar–H), 7.42 (d, J = 8.0 Hz, 1H, Ar–H), 6.78 (s, 1H, Pyrrole–H), 4.89 (s, 2H, Ar–CH_2O–). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 157.8, 137.2, 130.9, 130.8, 130.6, 130.4, 128.9, 124.9, 112.8, 105.7, 97.9, 75.7. HRMS, m/z 440.8228. Calcd for $C_{12}H_8Br_2Cl_2N_2O_2$, 440.8234.

*5.2.1.4.13. 4,5-Dibromo-1H-pyrrole-2-carboxylic acid (4-bromo-benzyloxy)-amide (**3m**).* Gray solid; yield 80.1%; mp 160–162 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.84 (s, 1H, Pyrrole–NH), 11.44 (brs, 1H, –CONH–), 7.59 (d, J = 8.0 Hz, 2H, Ar–H), 7.39 (d, J = 8.0 Hz, 2H, Ar–H), 6.78 (d, J = 2.4 Hz, 1H, Pyrrole–H), 4.86 (s, 2H, Ar–CH_2O–). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 157.7, 135.3, 131.2 (2C), 131.0 (2C), 125.1, 121.5, 112.8, 105.5, 97.9, 76.4. HRMS, m/z 450.8114. Calcd for $C_{12}H_9Br_3N_2O_2$, 450.8121.

*5.2.1.4.14. 4,5-Dibromo-1H-pyrrole-2-carboxylic acid (2-cyano-benzyloxy)-amide (**3n**).* Gray solid; yield 46.1%; mp 193–195 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.86 (s, 1H, Pyrrole–NH), 11.51 (brs, 1H, –CONH–), 7.87 (d, J = 6.8 Hz, 1H, Ar–H), 7.70–7.74 (m, 2H, Ar–H), 7.58 (d, J = 6.8 Hz, 1H, Ar–H), 6.78 (s, 1H, Pyrrole–H), 5.06 (s, 2H, Ar–CH_2O–). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 157.8, 138.9, 133.2, 132.9, 130.8, 129.3, 124.9, 117.2, 112.9, 112.1, 105.6, 97.9, 74.7. HRMS, m/z 397.8971. Calcd for $C_{13}H_9Br_2N_3O_2$, 397.8968.

*5.2.1.4.15. 4,5-Dibromo-1H-pyrrole-2-carboxylic acid (3-cyano-benzyloxy)-amide (**3o**).* Gray solid; yield 40.1%; mp 190–192 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.87 (s, 1H, Pyrrole–NH), 11.50 (brs, 1H, –CONH–), 7.92 (s, 1H, Ar–H), 7.76–7.83 (m, 2H, Ar–H), 7.59–7.62 (m, 1H, Ar–H), 6.79 (s, 1H, Pyrrole–H), 4.95 (s, 2H, Ar–CH_2O–). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 157.8, 137.7, 133.4, 132.0, 131.9, 129.5, 125.0, 118.6, 112.9, 111.3, 105.6, 97.9, 76.1. HRMS, m/z 397.8971. Calcd for $C_{13}H_9Br_2N_3O_2$, 397.8968.

*5.2.1.4.16. 4,5-Dibromo-1H-pyrrole-2-carboxylic acid (4-cyano-benzyloxy)-amide (**3p**).* Gray solid; yield 35.2%; mp 212–214 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.87 (s, 1H, Pyrrole–NH), 11.52 (brs, 1H, –CONH–), 7.86 (d, J = 8.0 Hz, 2H, Ar–H), 7.64 (d, J = 8.0 Hz, 2H, Ar–H), 6.78 (s, 1H, Pyrrole–H), 4.98 (s, 2H, Ar–CH_2O–). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 157.8, 141.6, 132.2 (2C), 129.2 (2C), 124.9, 118.7, 112.9, 110.8, 105.7, 97.9, 76.3. HRMS, m/z 397.8968. Calcd for $C_{13}H_9Br_2N_3O_2$, 397.8968.

*5.2.1.4.17. 4,5-Dibromo-1H-pyrrole-2-carboxylic acid (4-nitro-benzyloxy)-amide (**3q**).* Gray solid; yield 60.6%; mp 191–193 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.88 (s, 1H, Pyrrole–NH), 11.56 (s, 1H, –CONH–), 8.25 (d, J = 8.4 Hz, 2H, Ar–H), 7.73 (d, J = 8.4 Hz, 2H, Ar–H), 6.79 (d, J = 2.4 Hz, 1H, Pyrrole–H), 5.04 (s, 2H, Ar–CH_2O–). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 157.8, 147.2, 143.7, 129.5 (2C), 124.9, 123.3 (2C), 112.9, 105.7, 97.9, 76.0. HRMS, m/z 417.8859. Calcd for $C_{12}H_9Br_2N_3O_4$, 417.8867.

*5.2.1.4.18. 2-{2-[(4,5-Dibromo-1H-pyrrole-2-carbonyl)-amino-oxymethyl]-phenyl}-3-methoxy-acrylic acid methyl ester (**3r**).* Light yellow oil; yield 32.6%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.85 (s, 1H, Pyrrole–NH), 11.43 (brs, 1H, –CONH–), 7.65 (s, 1H, =$CHOCH_3$), 7.56 (d, J = 7.2 Hz, 1H, Ar–H), 7.30–7.35 (m, 2H, Ar–H), 7.09 (d, J = 7.2 Hz, 1H, Ar–H), 6.79 (s, 1H, Pyrrole–H), 4.73 (s, 2H, Ar–CH_2O–), 3.77 (s, 3H, –OCH_3), 3.57 (s, 3H, –OCH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 166.9, 160.8, 157.6, 134.9, 132.1, 130.8, 128.2, 127.5, 127.4, 125.2, 112.8, 108.4, 105.4, 97.8, 74.7, 61.7, 51.2. HRMS, m/z 486.9330. Calcd for $C_{17}H_{16}Br_2N_2O_5$, 486.9333.

*5.2.1.4.19. 1H-Pyrrole-2-carboxylic acid (3-methoxy-4-prop-2-ynyloxy-benzyloxy)-amide (**2a**).* White solid; yield 58.8%; mp 129–131 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.58 (s, 1H, Pyrrole–NH), 11.24 (brs, 1H, –CONH–), 7.10 (s, 1H, H-9), 7.02 (d, J = 8.0 Hz, 1H, H-12), 6.95 (d, J = 8.0 Hz, 1H, H-13), 6.92 (s, 1H, H-4), 6.71 (s, 1H, H-2), 6.09 (s, 1H, H-3), 4.83 (s, 2H, H-7), 4.79 (s, 2H, H-14), 3.78 (s, 3H, H-17), 3.55 (s, 1H, H-16). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 159.7 (s, C-6), 148.9 (s, C-10), 146.4 (s, C-11), 129.6 (s, C-8), 123.1 (s, C-5), 122.0 (d, C-4), 121.1 (d, C-13), 113.6 (d, C-12), 112.8 (d, C-9), 110.3 (d, C-2), 108.6 (d, C-3), 79.2 (s, C-15), 78.2 (d, C-16), 77.1 (t, C-7), 55.9 (t, C-14), 55.4 (q, C-17). HRMS, m/z 323.1004. Calcd for $C_{16}H_{16}N_2O_4$, 323.1002 $[M + Na]^+$.

*5.2.1.4.20. 1H-Pyrrole-2-carboxylic acid (4-fluoro-benzyloxy)-amide (**2g**).* Gray solid; yield 76.9%; mp 144–146 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 11.58 (s, 1H, Pyrrole–NH), 11.27 (brs, 1H, –CONH–), 7.48–7.51 (m, 2H, Ar–H), 7.19–7.24 (m, 2H, Ar–H), 6.91 (s, 1H, Pyrrole–H), 6.68 (s, 1H, Pyrrole–H), 6.08 (d, J = 2.4 Hz, 1H, Pyrrole–H), 4.87 (s, 2H, Ar–CH_2O–). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 163.2 (Ar–F), 160.7 (Ar–F), 159.7, 132.4, 131.0 (2C), 123.0, 122.1, 115.0 (2C), 110.2, 108.6, 76.4. HRMS, m/z 257.0701. Calcd for $C_{12}H_{11}FN_2O_2$, 257.0697 $[M + Na]^+$.

*5.2.1.4.21. 3-Methoxy-2-{2-[(1H-pyrrole-2-carbonyl)-amino-oxymethyl]-phenyl}-acrylic acid methyl ester (**2r**).* Light yellow oil; yield 56.6%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.59 (s, 1H, Pyrrole–NH), 11.25 (brs, 1H, –CONH–), 7.67 (s, 1H, =$CHOCH_3$), 7.64 (d, J = 7.2 Hz, 1H, Ar–H), 7.31–7.36 (m, 2H, Ar–H), 7.12 (d, J = 7.2 Hz, 1H, Ar–H), 6.93 (s, 1H, Pyrrole–H), 6.72 (s, 1H, Pyrrole–H), 6.11 (s, 1H, Pyrrole–H), 4.79 (s, 2H, Ar–CH_2O–), 3.78 (s, 3H, –OCH_3), 3.60 (s, 3H, –OCH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 166.9, 160.8, 159.7, 135.3, 131.8, 130.8, 128.0, 127.3 (2C), 123.1, 122.0, 110.3, 108.6, 108.5, 74.7, 61.7, 51.1. HRMS, m/z 353.1101. Calcd for $C_{17}H_{18}N_2O_5$, 353.1108 $[M + Na]^+$.

*5.2.1.4.22. 3,4,5-Tribromo-1H-pyrrole-2-carboxylic acid (3-methoxy-4-prop-2-ynyloxy-benzyloxy)-amide (**4a**).* White solid; yield 39.0%; mp 142–144 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 13.13 (s, 1H, Pyrrole–NH), 11.08 (brs, 1H, –CONH–), 7.08 (s, 1H, Ar–H), 7.01 (d, J = 8.0 Hz, 1H, Ar–H), 6.97 (d, J = 8.0 Hz, 1H, Ar–H), 4.82 (s, 2H, Ar–CH_2O–), 4.78 (d, J = 2.0 Hz, 2H, Ar–OCH_2–), 3.78 (s, 3H, Ar–OCH_3), 3.54 (s, 1H, alkynyl-H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 157.3, 148.8, 146.5, 129.1, 124.2, 121.3, 113.5, 112.8, 104.7, 102.0, 100.1, 79.2, 78.2, 77.1, 55.9, 55.4. HRMS, m/z 558.8296. Calcd for $C_{16}H_{13}Br_3N_2O_4$, 558.8297 $[M + Na]^+$.

*5.2.1.4.23. 3,4,5-Tribromo-1H-pyrrole-2-carboxylic acid (4-fluoro-benzyloxy)-amide (**4g**).* Gray solid; yield 45.4%; mp 172–174 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 13.16 (brs, 1H, Pyrrole–NH), 11.14 (s, 1H, –CONH–), 7.49–7.52 (m, 2H, Ar–H), 7.19–7.24 (m, 2H, Ar–H), 4.87 (s, 2H, Ar–CH_2O–). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 163.2 (Ar–F), 160.8 (Ar–F), 157.4, 132.0, 131.2 (2C), 124.1, 115.0 (2C), 104.9, 102.0, 100.1, 76.3. HRMS, m/z 492.7999. Calcd for $C_{12}H_8Br_3FN_2O_2$, 492.7992 $[M + Na]^+$.

*5.2.1.4.24. 3-Methoxy-2-{2-[(3,4,5-tribromo-1H-pyrrole-2-carbonyl)-aminooxymethyl]-phenyl}-acrylic acid methyl ester (**4r**).* White solid; yield 34.7%; mp 179–181 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 13.15 (s, 1H, Pyrrole–NH), 11.02 (brs, 1H, –CONH–), 7.68 (s, 1H, =$CHOCH_3$), 7.56 (d, J = 7.2 Hz, 1H, Ar–H), 7.31–7.34 (m, 2H, Ar–H), 7.10 (d, J = 7.2 Hz, 1H, Ar–H), 4.75 (s, 2H, Ar–CH_2O–), 3.80 (s, 3H, –OCH_3), 3.60 (s, 3H, –OCH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 166.9, 160.9, 157.1, 134.7, 132.0, 130.9, 128.2, 127.6, 127.4, 124.0, 108.4, 104.8, 102.1, 100.2, 74.7, 61.7, 51.2. HRMS, m/z 588.8397. Calcd for $C_{17}H_{15}Br_3N_2O_5$, 588.8403 $[M + Na]^+$.

*5.2.1.4.25. 4,5-Dichloro-1H-pyrrole-2-carboxylic acid (3-methoxy-4-prop-2-ynyloxy-benzyloxy)-amide (**5a**).* Yellow solid; yield 41.8%; mp 169–171 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.90 (s, 1H,

Pyrrole–NH), 11.45 (brs, 1H, –CONH–), 7.08 (s, 1H, Ar–H), 7.02 (d, J = 8.4 Hz, 1H, Ar–H), 6.93 (d, J = 8.4 Hz, 1H, Ar–H), 6.77 (s, 1H, Pyrrole–H), 4.81 (s, 2H, Ar–CH_2O–), 4.78 (s, 2H, Ar–OCH_2–), 3.77 (s, 3H, Ar–OCH_3), 3.55 (s, 1H, alkynyl-H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 157.7, 148.9, 146.5, 129.2, 121.9, 121.2, 115.6, 113.5, 112.8, 109.7, 108.0, 79.2, 78.2, 77.2, 55.9, 55.3. HRMS, m/z 391.0232. Calcd for $C_{16}H_{14}Cl_2N_2O_4$, 391.0223 $[M + Na]^+$.

*5.2.1.4.26. 4,5-Dichloro-1H-pyrrole-2-carboxylic acid (4-fluorobenzyloxy)-amide (**5g**).* Yellow solid; yield 69.5%; mp 123–125 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.96 (brs, 1H, Pyrrole–NH), 11.55 (brs, 1H, –CONH–), 7.51–7.54 (m, 2H, Ar–H), 7.23–7.28 (m, 2H, Ar–H), 6.81 (s, 1H, Pyrrole–H), 4.91 (s, 2H, Ar–CH_2O–). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 163.2 (Ar–F), 160.8 (Ar–F), 157.7, 132.1, 131.2 (2C), 121.8, 115.7, 115.1 (2C), 109.8, 108.0, 76.5. HRMS, m/z 324.9921. Calcd for $C_{12}H_9Cl_2FN_2O_2$, 324.9917 $[M + Na]^+$.

*5.2.1.4.27. 2-{2-[(4,5-Dichloro-1H-pyrrole-2-carbonyl)-amino-oxymethyl]-phenyl}-3-methoxy-acrylic acid methyl ester (**5r**).* Light yellow oil; yield 53.5%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.89 (s, 1H, Pyrrole–NH), 11.45 (brs, 1H, –CONH–), 7.64 (s, 1H, =$CHOCH_3$), 7.55–7.58 (m, 1H, Ar–H), 7.30–7.37 (m, 2H, Ar–H), 7.07–7.10 (m, 1H, Ar–H), 6.75 (s, 1H, Pyrrole–H), 4.73 (s, 2H, Ar–CH_2O–), 3.77 (s, 3H, –OCH_3), 3.57 (s, 3H, –OCH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 166.9, 160.8, 157.7, 134.9, 132.0, 130.8, 128.2, 127.5, 127.4, 121.9, 115.6, 109.9, 108.5, 108.0, 74.7, 61.7, 51.1. HRMS, m/z 421.0327. Calcd for $C_{17}H_{16}Cl_2N_2O_5$, 421.0328 $[M + Na]^+$.

*5.2.1.5. Synthetic procedures for compounds **2aa**, **2ab**.* Compound **2aa** and **2ab** were synthesized as follows: To a solution of compound **2a** (0.1 g, 0.33 mmol) in dry DMF (20.0 mL) potassium carbonate (1.0 g, 7.2 mmol) was added and stirred. 10 min later, two drops of CH_3I was added to the above solution. The mixture was stirred for 5 h at room temperature [5]. Then the suspension was extracted with ethyl acetate/water system. Separating the organic layer, the solvent was removed by distillation to give the crude residue. **2aa** and **2ab** were isolated from the residue by flash chromatography on silica gel eluting with ethyl acetate/petroleum [elution solvent: ethyl acetate/petroleum ether (60–90 °C), v/v = 1:8]. Respective substituents at the benzene ring were listed in Scheme 2 and Table 1.

*5.2.1.5.1. 1H-Pyrrole-2-carboxylic acid (3-methoxy-4-prop-2-ynyloxy-benzyloxy)-methyl-amide (**2aa**).* Light yellow solid; yield 60.1%; mp 99–101 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.86 (brs, 1H, Pyrrole–NH), 6.98 (d, J = 8.0 Hz, 1H, Ar–H), 6.87–6.89 (m, 2H, Ar–H), 6.87–6.89 (m, 2H, Pyrrole–H), 6.16–6.19 (m, 1H, Pyrrole–H), 4.79 (s, 2H, Ar–CH_2O–), 4.70 (d, J = 2.4 Hz, 2H, Ar–OCH_2–), 3.80 (s, 3H, Ar–OCH_3), 3.28 (s, 3H, –$CONCH_3$), 2.45 (s, 1H, alkynyl-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.7, 148.6, 146.2, 127.1, 122.5, 121.0, 120.9, 114.3, 112.9, 111.8, 109.3, 77.2, 75.2, 75.0, 55.6, 54.9, 33.7. HRMS, m/z 337.1165. Calcd for $C_{17}H_{18}N_2O_4$, 337.1159 $[M + Na]^+$.

*5.2.1.5.2. 1-Methyl-1H-pyrrole-2-carboxylic acid (3-methoxy-4-prop-2-ynyloxy-benzyloxy)-methyl-amide (**2ab**).* Light yellow solid; yield 20.0%; mp 94–96 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.99 (d, J = 8.0 Hz, 1H, Ar–H), 6.88 (s, 1H, Ar–H), 6.86 (d, J = 8.0 Hz, 1H, Ar–H), 6.83 (s, 1H, Pyrrole–H), 6.71 (s, 1H, Pyrrole–H), 6.08–6.09 (m, 1H, Pyrrole–H), 4.76 (s, 2H, Ar–CH_2O–), 4.76 (s, 2H, Ar–OCH_2–), 3.84 (s, 3H, Ar–OCH_3), 3.81 (s, 3H, Pyrrole-NCH_3), 3.34 (s, 3H, –$CONCH_3$), 2.51 (s, 1H, alkynyl-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.9, 149.5, 147.1, 128.4, 127.8, 123.6, 122.0, 116.5, 113.7, 113.1, 107.1, 78.3, 75.9, 75.8, 56.6, 55.8, 36.8, 35.1. HRMS, m/z 351.1316. Calcd for $C_{18}H_{20}N_2O_4$, 351.1315 $[M + Na]^+$.

5.3. Antifungal activity

The fungicidal activities of the compounds **3a**–**r**, **2a**, **2g**, **2r**, **4a**, **4g**, **4r**, **5a**, **5g**, **5r**, **2aa**, **2ab** were tested in vitro against *A. solani*, *C. arachidicola*, *F. omysporum*, *G. zeae* and *P. piricola* and their relative inhibitory ratio (%) had been determined by using the mycelium growth rate method [30]. Anthranilamide and fenpiclonil were used as control. After the mycelia grew completely, the diameter of the mycelia was measured and the inhibition rate was calculated according to the formula:

I=($D1$–$D2$)/D1 × 100% where I was the inhibition rate, D1 was the average diameter of mycelia in the blank test, and D2 was the average diameter of mycelia in the presence of those compounds. The inhibition ratio of those compounds at the dose of 50 μg mL^{-1} was summarized in Table 2. The EC_{50} values of compounds **2a**, **3a** and fenpiclonil had been experimented and calculated by the Scatchard method. And the results were summarized in Table 3.

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