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Design, synthesis, and bioactivity of nortopsentin analogues containing 1,2,4-triazole moieties

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Abstract

Plant diseases are serious and difficult to control. Novel and efficient pesticides are urgently needed. A series of nortopsentin analogues were designed, synthesized, and evaluated for their antiviral activities and fungicidal activities. Compound **3g** with higher antiviral activity than nortopsentin D and ribavirin emerged as new antiviral lead compound. Further fungicidal activity tests revealed that nortopsentin analogues displayed broad-spectrum fungicidal activities. Compounds **3a**, **3d**, and **3f** displayed higher antifungal activities against *Cercospora arachidicola Hori* than commercial fungicides carbendazim and chlorothalonil. Current research has laid a foundation for the application of nortopsentin analogues in plant protection.

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1 | INTRODUCTION

Viral diseases are the second most serious plant diseases after fungi in agricultural production, and most crops around the world are harmed to varying degrees. Plant viruses are absolutely parasitic in plant cells, and the materials, energy, and sites required for their replication are provided by host cells. Because plants do not have a complete immune system, it is difficult to control plant viral diseases, which has always been a difficult and hot issue in plant diseases and virology research.[1–3] Tobacco mosaic virus (TMV), named for its first discovery in tobacco, is the earliest discovered and most studied virus. It is often used as a model virus in the development of antiviral agents. Besides harming tobacco, TMV can also infect more than 400 crops such as tomato, eggplant, potato, pepper, and *Solanum nigrum*.[4,5] The existing antiviral agents can only give moderate control effect (antiviral agent ribavirin in Figure 1: less than 50% anti-TMV effect at 500 μg/mL), and the treatment effect is poor. The prevention and treatment of viral diseases has a long way to go.[6]

Natural products are the source of pesticide discovery. However, the probability that a natural product directly isolated from organisms can be directly used as a pesticide for treating diseases is very low. Using these "basic molecules" as structures to synthesize variants of active molecules is an absolutely feasible way to develop pesticides because of their immense structural diversity and wide variety of biological activities.[7–10]

Bisindole alkaloids are a family of very important natural products isolated from marine organisms. Nortopsentins A to D (Figure 1) are one of the important marine alkaloids. Biological activity research revealed that nortopsentins A to D displayed interesting biological activities such as cytotoxicity against P388 cells and antifungal activity against *Candida albicans*.[11–13] A series of nortopsentin analogues were reported in which the central imidazole ring was replaced by several five-membered heterocycles such as bis-indolylthiophenes,[14] -pyrazole,[15] -oxazoles,[16] -isoxazoles,[17] -furans,[17] -pyrroles,[18] -thiazoles,[19,20] and -1,2,4-oxadiazoles.[21] In the previous work, we found that nortopsentin alkaloids had good antiviral activities against plant viruses for the first time.[22] On the other hand, 1,2,4-triazole ring system is an important five-membered heterocycle ring found in many molecules with significant biological activity.[23–25] Considering the above findings, we designed and synthesized a series of nortopsentin analogues containing 1,2,4-triazole ring system (Figure 2). The antiviral activities, fungicidal activities, and structure-activity relationships were evaluated systematically.

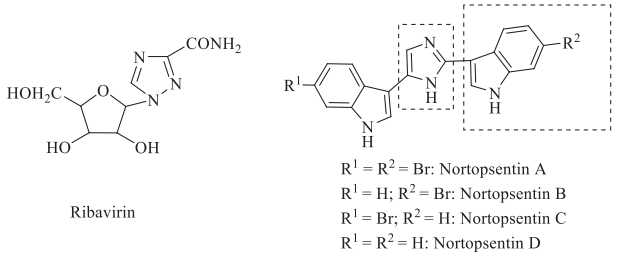


FIGURE 1 Structures of ribavirin and nortopsentins A to D

2 | RESULTS AND DISCUSSION

2.1 | Chemistry

According to previous structure-activity relationships,[22] nortopsentin analogues **3a**-**3j** were designed and obtained by one-step condensation reaction (Scheme 1) of commercially available 1*H*-indole-3-carbonitrile and corresponding acylhydrazines **2a**-**2j**. As previously reported,[26] some 1,2,4-triazoles also exhibit tautomerism (Figure 3). ^{1}H NMR spectrum of nortopsentin **3b** showed a splitting of all signals, which could be suppressed by the addition of 1% of CF_3COOH into the deuterated solvent.

2.2 | Phytotoxic activity

The phytotoxic-activity tests showed that the nortopsentin analogues **3a**-**3j** were safe for testing on plants at 500 μg/mL. The detailed test procedures can be seen in the Supporting Information.

2.3 | Antiviral activity in vivo

The results of the anti-TMV activities of the nortopsentin analogues **3a**-**3j** are listed in Table 1 with nortopsentin D and the commercial plant virucide ribavirin as the controls. The inactive activities of all compounds listed in Table 1 at 500 μg/mL were first tested, and the curative activities and protective activities of compounds with good inactive activities (inactive effect: less than 40%) were further tested.

As depicted in Table 1, the nortopsentin analogues **3a**-**3j** containing 1,2,4-triazole showed good antiviral activities in vivo. Compound **3e** showed the same level of biological activity as nortopsentin D but higher than ribavirin. Among these compounds, compound **3g** displayed the best antiviral activity, which is higher than that of nortopsentin D and ribavirin. Compared with nortopsentin D, **3a** exhibited relatively low activity. The

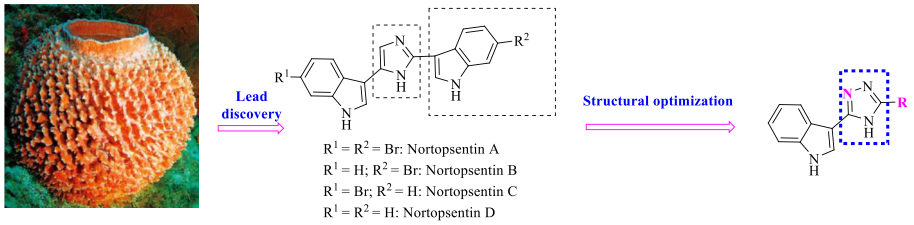
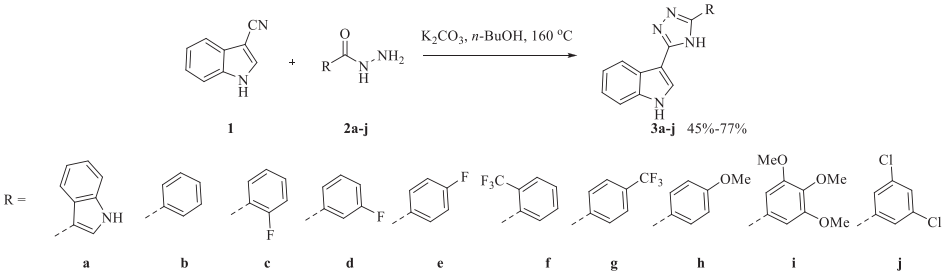


FIGURE 2 Design of nortopsentin analogues [Color figure can be viewed at wileyonlinelibrary.com]



SCHEME 1 Synthesis of **3a-3j**

FIGURE 3 Tautomerization of 1,2,4-triazole

TABLE 1 In vivo antiviral activities of compounds **3a−3j**, nortopsentin D and ribavirin against TMV.

Compd	Concn (μg/mL)	Inactive effect (%)[a]	Curative effect (%)[a]	Protective effect (%)[a]
3a	500	28±3	—	—
3b	500	40±1	32±3	36±2
	100	10±1	6±2	10±1
3c	500	14±3	—	—
3d	500	10±3	—	—
3e	500	45±4	42±3	39±1
	100	19±1	17±2	11±3
3f	500	23±1	—	—
3g	**500**	**48±1**	**42±2**	**45±3**
	100	**23±2**	**20±1**	**22±1**
3h	500	9±3	—	—
3i	500	8±2	—	—
3j	500	33±3	—	—
Nortopsentin D	500	45±2	40±3	37±1
	100	20±2	17±2	12±1
Ribavirin	500	38±1	36±2	37±2
	100	12±1	11±1	9±2

Abbreviation: TMV, tobacco mosaic virus. Activity data with prominent were presented in bold.

[a]Average of three replicates; All results are expressed as mean ± SD.

substitution of benzene ring for indole ring is beneficial to the improvement of biological activity (inhibitory effect: **3b** > **3a**). The introduction of fluorine atom in the *ortho*- and *meta*-position of benzene ring would lead to a sharp decrease in activity (inhibitory effect: **3b** > **3c**, **3d**), and the introduction of fluorine atom in the *para*-position would be beneficial to the improvement of activity (inhibitory effect: **3e** > **3b**). The introduction of trifluoromethyl at the *ortho*-position of benzene ring leads to a decrease in activity (inhibitory effect: **3b** > **3f**), while the introduction of trifluoromethyl at the *para*-position is beneficial to the improvement of activity (inhibitory effect: **3g** > **3b**). Compounds **3h-3j** displayed lower antiviral activities than **3b**, which indicated that the introduction of chlorine atom and methoxy group are bad for activity. From the above structure-activity relationship, it can be seen that the 1,2,4-triazole ring and benzene ring regions are very sensitive, and minor changes will have a great impact on the activity.

2.3.1 | In vitro fungicidal activity

Nortopsentin analogues **3a-3j** were also evaluated for their fungicidal activities with nortopsentin D and commercial fungicides carbendazim and chlorothalonil as controls.

The fungicidal activities of **3a-3j** were evaluated in mycelial growth tests[27] conducted in artificial media against 14 plant pathogens at a rate of 50 μg/mL. The results showed that these compounds also exhibited broad-spectrum fungicidal activities (Table 2). Compounds **3a-3j** displayed higher antifungal activities than

TABLE 2 In vitro fungicidal activities of compounds **3a**-**3j**, nortopsentin D, carbendazim, and chlorothalonil against 14 kinds of fungi

	Fungicidal Activities (%)[a]/50 μg/mL													
Compound	***F.C***	***C.H***	***P.P***	***R.C***	***B.M***	***W.A***	***F.M***	***A.S***	***F.G***	***P.I***	***P.C***	***S.S***	***R.S***	***B.C***
3a	16 ± 2	**60 ± 1**	35 ± 3	33 ± 3	14 ± 2	24 ± 1	13 ± 1	48 ± 3	16 ± 1	16 ± 1	20 ± 2	46 ± 1	56 ± 2	13 ± 1
3b	28 ± 1	48 ± 3	**83 ± 2**	46 ± 1	25 ± 1	47 ± 2	33 ± 2	48 ± 2	37 ± 2	32 ± 2	47 ± 1	53 ± 2	47 ± 3	49 ± 2
3c	16 ± 1	28 ± 2	23 ± 1	24 ± 2	14 ± 2	12 ± 3	8 ± 1	15 ± 1	8 ± 1	13 ± 1	10 ± 2	41 ± 1	38 ± 2	14 ± 1
3d	38 ± 3	**68 ± 1**	**63 ± 1**	**71 ± 1**	28 ± 3	44 ± 2	42 ± 2	59 ± 3	33 ± 2	36 ± 2	43 ± 1	**73 ± 2**	56 ± 3	71 ± 2
3e	28 ± 2	32 ± 1	21 ± 2	42 ± 1	17 ± 2	27 ± 1	13 ± 1	26 ± 2	14 ± 1	23 ± 1	27 ± 2	43 ± 3	38 ± 2	51 ± 1
3f	31 ± 1	**72 ± 3**	56 ± 1	**65 ± 2**	50 ± 1	**62 ± 2**	54 ± 1	56 ± 3	35 ± 2	**61 ± 3**	43 ± 3	**75 ± 2**	59 ± 3	59 ± 2
3g	19 ± 2	48 ± 1	4 ± 2	38 ± 2	22 ± 1	24 ± 1	33 ± 2	41 ± 1	37 ± 3	23 ± 2	17 ± 2	**64 ± 1**	41 ± 2	51 ± 1
3h	28 ± 1	52 ± 2	**88 ± 3**	53 ± 3	33 ± 2	47 ± 2	33 ± 1	48 ± 1	43 ± 2	36 ± 1	47 ± 1	**66 ± 1**	50 ± 1	**61 ± 2**
3i	21 ± 2	27 ± 1	37 ± 2	46 ± 3	23 ± 1	30 ± 3	24 ± 2	45 ± 2	39 ± 1	27 ± 2	16 ± 2	48 ± 2	38 ± 2	23 ± 1
3j	19 ± 1	36 ± 2	15 ± 1	30 ± 1	14 ± 2	9 ± 2	17 ± 1	26 ± 2	0	16 ± 1	17 ± 1	52 ± 2	38 ± 1	44 ± 2
Nortopsentin D	26 ± 1	29 ± 2	58 ± 1	26 ± 2	21 ± 1	42 ± 2	9 ± 1	33 ± 1	10 ± 1	16 ± 2	3 ± 1	39 ± 2	14 ± 1	7 ± 1
Carbendazim[b]	77 ± 2	58 ± 2	54 ± 1	78 ± 2	72 ± 2	90 ± 1	84 ± 1	56 ± 2	88 ± 2	83 ± 1	90 ± 2	100	100	96 ± 1
Chlorothalonil[b]	97 ± 1	11 ± 2	96 ± 2	98 ± 1	97 ± 2	97 ± 1	79 ± 2	56 ± 1	100	100	55 ± 2	100	27 ± 1	100

Abbreviations: *A.S*, *Alternaria solani*; *B.C*, *Botrytis cinerea*; *B.M*, *Bipolaris maydis*; *C.H*, *Cercospora arachidicola Hori*; *F.C*, *Fusarium oxysporum f. sp. cucumeris*; *F.G*, *Fusarium graminearum*; *F.M*, *Fusarium moniliforme*; *P.C*, *Phytophthora capsici*; *P.I*, *Phytophthora infestans*; *P.P*, *Physalospora piricola*; *R.C*, *Rhizoctonia cerealis*; *R.S*, *Rhizoctonia solani*; *S.S*, *Sclerotinia sclerotiorum*; *W.A*, *Watermelon anthracnose*. Activity data with prominent were presented in bold.

[a]Average of three replicates; all results are expressed as mean ± SD.

[b]The commercial agricultural fungicides were used for comparison of antifungal activity.

nortopsentin D against most of the 14 plant pathogens. Compounds **3a**, **3d**, and **3f** displayed higher antifungal activities against *Cercospora arachidicola Hori* than commercial fungicides carbendazim and chlorothalonil. Compounds **3b**, **3d**, and **3h** showed higher antifungal activities against *Physalospora piricola* than commercial fungicide carbendazim. Different from the rule of antiviral activity, *m*-fluorobenzene ring compound **3d** and *o*-trifluoromethyl compound **3f** displayed relatively higher antifungal activities against most of the 14 plant pathogens (inhibitory effect: **3d** > **3c**, **3e**; **3f** > **3g**).

In summary, nortopsentin analogues **3a-3j** were designed, synthesized, and evaluated for their antiviral activities and fungicidal activities. Compound **3e** showed the same level of biological activity as nortopsentin D but higher than ribavirin. Compound **3g** with higher antiviral activity than nortopsentin D and ribavirin emerged as new antiviral lead compound. Further fungicidal test reveal that these compounds displayed broad-spectrum fungicidal activities against 14 kinds of plant fungi at 50 μg/mL. Compounds **3a-3j** displayed higher antifungal activities than nortopsentin D against most of the 14 plant pathogens. Compounds **3a**, **3d**, and **3f** displayed higher antifungal activities against *Cercospora arachidicola Hori* than commercial fungicides carbendazim and chlorothalonil. Current research has laid a foundation for the application of nortopsentin analogues in plant protection.

3 | EXPERIMENTAL

3.1 | Chemistry

The reagents were purchased from commercial sources and were used as received. All anhydrous solvents were dried and purified by standard techniques prior to use. The melting points of the compounds were tested on an X-4 binocular microscope (Beijing Tech Instruments Company). NMR spectra were obtained with a Bruker AV 400 spectrometer (Bruker Co., Fallanden, Switzerland) with either $CDCl_3$ or DMSO-d_6 as the solvent. High-resolution mass spectra were obtained with an FT-ICR mass spectrometer (Ionspec, 7.0 T, Kuala Lumpur, Malaysia).

3.1.1 | General procedures for the preparation of compounds 3a-3j

The mixture of 1*H*-indole-3-carbonitrile (**1**, 1 g, 7 mmol), corresponding acylhydrazines **2a-2j** (3.5 mmol) and K_2CO_3 (0.48 g, 3.5 mmol) in *n*-BuOH (10 mL) was stirred at 160°C for 8 hours. Then, the mixture was allowed to reach room temperature and taken into water (50 mL). The resulting solution was extracted with ethyl acetate (3 × 50 mL). The combined organic phases were washed with brine (100 mL), dried over anhydrous Na_2SO_4,

filtered, and concentrated in vacuo. The residue was purified by flash chromatography on a silica gel using petroleum ether and ethyl acetate (2:1, v/v) as the eluent to give **3a-3j**.

3,5-Di(1*H*-indol-3-yl)-4*H*-1,2,4-triazole (3a)

Yellow solid; yield 77%; mp 217°C to 219°C; ^{1}H NMR (400 MHz, DMSO-d_6) *isomers* δ 13.70 (s, 0.38H, NH), 11.69 and 11.63 (s, 1H, NH), 11.52 and 11.39 (s, 1H, NH), 11.09 (s, 0.52H, NH), 8.55-7.79 (m, 4H, Ar-H), 7.45-7.50 (m, 2H, Ar-H), 7.16-7.21 (m, 4H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6) *isomers* δ 162.4, 137.5, 136.9, 130.0, 129.9, 125.6, 125.4, 123.0, 122.5, 121.0, 120.7, 112.3. $C_{18}H_{14}N_5$ $[M + H]^+$ 300.1244, found (ESI^+) 300.1249.

3-(5-Phenyl-4*H*-1,2,4-triazol-3-yl)-1*H*-indole (3b)

Brick red solid; yield 58%; mp 151°C to 152°C; ^{1}H NMR (400 MHz, DMSO-d_6) *isomers* δ 14.25 and 13.98 (s, 1H, NH), 11.68 and 11.43 (s, 1H, NH), 8.38 and 8.31 (d, J = 6.1 Hz, 1H, Ar-H), 7.87-8.16 (m, 4H, Ar-H), 7.43-7.57 (m, 3H, Ar-H), 7.16-7.22 (m, 2H, Ar-H); ^{1}H NMR (400 MHz, DMSO-d_6, 1% TFA) δ 11.66 (s, 1H, NH), 8.36 (d, J = 7.1 Hz, 1H, Ar-H), 8.14 (d, J = 7.3 Hz, 2H, Ar-H), 8.05 (d, J = 2.0 Hz, 1H, NH), 7.88 (d, J = 7.3 Hz, 1H, Ar-H),7.46-7.56 (m, 4H, Ar-H), 7.20-7.23 (m, 2H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6, 1% TFA) δ 167.8, 136.3, 131.2, 129.21, 129.19, 128.8, 128.2, 127.4, 125.9, 125.7, 124.7, 122.1, 120.8, 120.2, 111.9. $C_{16}H_{13}N_4$ $[M + H]^+$ 261.1135, found (ESI^+) 261.1131.

3-(5-(2-Fluorophenyl)-4*H*-1,2,4-triazol-3-yl)-1*H*-indole (3c)

Brown solid; yield 65%; mp 165°C to 167°C; ^{1}H NMR (400 MHz, DMSO-d_6) *isomers* δ 14.13 and 14.10 (s, 1H, NH), 11.71 and 11.46 (s, 1H, NH), 8.36 (d, J = 8.7 Hz, 1H, Ar-H), 8.17-8.21 (m, 1H, Ar-H), 8.07 and 7.97 (s, 1H, Ar-H), 7.67-7.73 (m, 1H, Ar-H), 7.48-7.54 (m, 2H, Ar-H), 7.37 (d, J = 7.5 Hz, 1H, Ar-H), 7.21-7.28 (m, 2H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.7, 130.4, 130.2, 130.0, 125.7, 125.0, 124.5, 124.4, 122.3, 120.7, 120.4, 116.6, 116.3, 112.0, 103.2. $C_{16}H_{12}FN_4$ $[M + H]^+$ 279.1041, found (ESI^+) 279.1037.

3-(5-(3-Fluorophenyl)-4*H*-1,2,4-triazol-3-yl)-1*H*-indole (3d)

Brown solid; yield 72%; mp 156°C to 157°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 14.13 (s, 1H, NH), 11.72 (s, 1H, NH), 8.38 (s, 1H, Ar-H), 8.07 (s, 1H, Ar-H), 8.00 (d, J = 7.4 Hz, 1H, Ar-H), 7.87 (d, J = 9.8 Hz, 1H, Ar-H), 7.67-7.82 (m, 1H, Ar-H), 7.47-7.62 (m, 2H, Ar-H), 7.20-7.29 (m, 2H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6) *isomers* δ 163.6, 161.2, 136.3, 130.9, 130.8, 130.4, 130.3, 125.8, 124.6, 123.6, 122.3, 121.9, 120.7, 120.4, 118.2, 118.0, 114.35, 114.29, 114.12, 114.07, 112.0, 103.2. $C_{16}H_{12}FN_4$ $[M + H]^+$ 279.1041, found (ESI^+) 279.1043.

3-(5-(4-Fluorophenyl)-4*H*-1,2,4-triazol-3-yl)-1*H*-indole (3e)

Brown solid; yield 52%; mp 262°C to 264°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.21 (s, 1H, NH), 11.91 (s, 1H, NH), 8.46 (s, 1H, Ar-H), 8.26 (d, J = 2.0 Hz, 1H, Ar-H), 7.99-8.03 (m, 2H, Ar-H), 7.80 (dd, J = 5.9, 8.2 Hz, 1H, Ar-H), 7.64 (d, J = 7.7 Hz, 1H, Ar-H), 7.56 (d, J = 7.9 Hz, 1H, Ar-H), 7.24-7.40 (m, 2H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6) *isomers* δ 162.5, 147.2, 135.7, 134.9, 131.3, 130.9, 130.8, 130.7, 130.6, 129.8, 129.7, 127.2, 123.8, 122.1, 118.9, 116.8, 116.4, 116.3, 116.1, 116.0, 115.9, 115.8, 113.4. $C_{16}H_{12}FN_4$ $[M + H]^+$ 279.1041, found (ESI^+) 279.1046.

3-(5-(2-(Trifluoromethyl)phenyl)-4*H*-1,2,4-triazol-3-yl)-1*H*-indole (3f)

Yellow solid; yield 45%; mp 253°C to 254°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 14.20 (s, 1H, NH), 11.71 (s, 1H, NH), 8.33 (d, J = 7.7 Hz, 1H, Ar-H), 8.05 (d, J = 2.5 Hz, 1H, Ar-H), 8.01 (d, J = 7.6 Hz, 1H, Ar-H), 7.90 (d, J = 7.8 Hz, 1H, Ar-H), 7.80 (t, J = 7.2 Hz, 1H, Ar-H), 7.68 (d, J = 7.6 Hz, 1H, Ar-H), 7.52 (d, J = 7.9 Hz, 1H, Ar-H), 7.16-7.25 (m, 2H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.3, 152.4, 136.8, 132.7, 132.2, 129.6, 127.01, 127.00, 126.1, 125.2, 122.8, 121.1, 120.8, 112.5, 103.7. $C_{17}H_{12}F_3N_4$ $[M + H]^+$ 329.1009, found (ESI^+) 329.1015.

3-(5-(4-(Trifluoromethyl)phenyl)-4*H*-1,2,4-triazol-3-yl)-1*H*-indole (3g)

Yellow solid; yield 57%; mp 157°C to 158°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 14.24 (s, 1H, NH), 11.73 (s, 1H, NH), 8.36-8.42 (m, 2H, Ar-H), 8.08-8.17 (m, 2H, Ar-H), 7.84-7.90 (m, 3H, Ar-H), 7.52-7.74 (m, 1H, Ar-H), 7.24 (t, J = 3.7 Hz, 1H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6) *isomers* δ 166.9, 166.2, 136.3, 134.7, 131.7, 131.5, 130.1, 128.6, 128.3, 126.4, 125.8, 125.7, 125.6, 125.5, 125.23, 125.20, 124.7, 122.2, 120.7, 120.3, 112.0. $C_{17}H_{12}F_3N_4$ $[M + H]^+$ 329.1009, found (ESI^+) 329.1011.

3-(5-(4-Methoxyphenyl)-4*H*-1,2,4-triazol-3-yl)-1*H*-indole (3h)

Yellow solid; yield 74%; mp 183°C to 185°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.87 (s, 1H, NH), 11.54 (s, 1H, NH), 8.37 (d, J = 6.5 Hz, 1H, Ar-H), 8.02-8.08 (m, 2H, Ar-H), 7.86-7.94 (m, 1H, Ar-H), 7.42-7.51 (m, 1H, Ar-H),

7.21 (d, J = 5.4 Hz, 1H, Ar-H), 6.97-7.17 (m, 3H, Ar-H), 3.83 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6) *isomers* δ 167.0, 166.5, 165.4, 162.8, 162.0, 136.3, 136.2, 131.3, 129.3, 128.4, 127.4, 126.2, 124.8, 121.7, 121.1, 120.9, 120.3, 114.1, 113.8, 113.7, 113.3, 111.8, 111.7, 55.4, 55.2. $C_{17}H_{15}N_4O$ $[M + H]^+$ 291.1240, found (ESI^+) 291.1246.

3-(5-(3,4,5-Trimethoxyphenyl)-4*H*-1,2,4-triazol-3-yl)-1*H*-indole (3i)

Yellow solid; yield 63%; mp 242°C to 243°C; ^1H NMR (400 MHz, DMSO-d_6) δ 11.52 (s, 2H, NH), 8.13 (d, J = 7.7 Hz, 2H, Ar-H), 8.01 (d, J = 2.9 Hz, 2H, Ar-H), 7.41 (d, J = 7.9 Hz, 2H, Ar-H), 7.23 (s, 1H, Ar-H), 3.82 (s, 6H, OCH_3), 3.72 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6) *isomers* δ 167.4, 167.1, 153.1, 141.8, 136.7, 132.0, 129.1, 128.9, 126.7, 126.4, 122.3, 121.5, 120.8, 112.2, 110.9, 107.0, 65.5, 60.6, 56.4. $C_{19}H_{19}N_4O_3$ $[M + H]^+$ 351.1452, found (ESI^+) 351.1456.

3-(5-(3,5-Dichlorophenyl)-4*H*-1,2,4-triazol-3-yl)-1*H*-indole (3j)

Brown solid; yield 68%; mp 246°C to 248°C; ^1H NMR (400 MHz, DMSO-d_6) δ 14.28 (s, 1H, NH), 11.74 (s, 1H, NH), 8.36-8.38 (m, 1H, Ar-H), 8.05-8.11 (m, 3H, Ar-H), 7.70 (s, 1H, Ar-H), 7.48-7.55 (m, 1H, Ar-H), 7.23 (t, J = 3.6 Hz, 2H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.1, 136.3, 135.3, 134.6, 131.5, 128.1, 126.3, 125.9, 124.6, 124.1, 122.3, 120.7, 120.5, 112.0. $C_{16}H_{11}Cl_2N_4$ $[M + H]^+$ 329.0355, found (ESI^+) 329.0357.

3.1.2 | Biological Assay

Each test was repeated three times at 25 ± 1°C. Active effect expressed in percentage scale of 0 to 100 (0: no activity; 100: total inhibited).

Specific steps for the anti-TMV[28] and fungicidal[27] activities were carried out in accordance with the literature method, also can be seen in the Supporting Information.

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CONFLICT OF INTEREST

The authors declare no competing financial interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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