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Synthesis and fungicidal activity of tryptophan analogues – the unexpected calycanthaceous alkaloid derivatives

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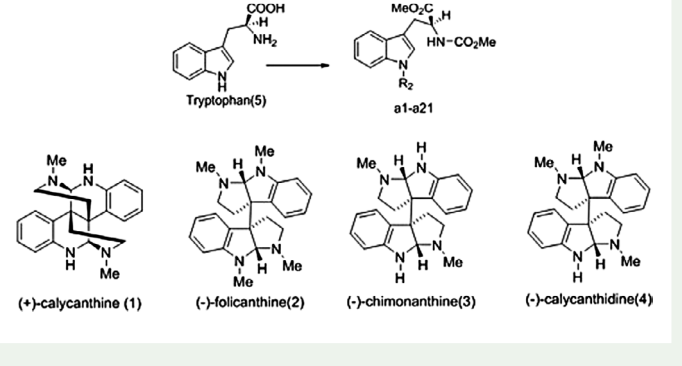
ABSTRACT

A series of 21 N-protected tryptophan derivatives were synthesised from tryptophan in good yields. Their structures were characterised by IR, ^{1}H NMR, ^{13}C NMR, DEPT (90° and 135°) and MS analysis. The synthesised compounds were evaluated against a wide variety of plant pathogen fungi. Compounds **a19** and **a21** displayed activity against *Fusarium oxysporum* (*F. oxysporum*), and compound **a21** showed high activity against *F. oxysporum* and *Eggplant Verticillium*, with EC_{50} values of 58.27 and 77.39 μg mL^{-1}, respectively. Considering that the bioassay of the title compounds was evaluated, effects of the chain alkyl substituents may contribute to the significant variations in fungicidal potency. Their structure–antifungal activity relationships were also discussed. These results will pave the way for further design, structural modification and development of calycanthaceous alkaloids as antimicrobial agents.



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1. Introduction

Natural products with novel scaffolds always afford an opportunity to discover novel antimicrobial agents that operate by modes of action different from those that are already known. Consequently, the resulting new agrochemicals have the opportunity to overcome resistance to chemicals currently in use (Walter 2002; Newman & Cragg 2007; Lin et al. 2012). Calycanthaceous alkaloids (Zhang, Li, Ji et al. 2009; Xiang et al. 2010) (Figure 1), mainly distributed in China, North America and Australia (Kozomara et al. 2008; Zhang et al. 2014), are an important class of alkaloid that can be isolated from roots, leaves, flowers and fruits of chimonanthus praecox (Liu et al. 2008). These compounds have demonstrated important biological activities such as anticonvulsant, antifungal, antiviral, analgesic, anti-tumour and melanogenesis inhibitory properties (Zhang, Gao et al. 2009; Lv et al. 2012; Araki et al. 2013; Gui et al. 2014). Because of their broad spectrum of biological properties, a number of studies aimed at the synthesis and antimicrobial activity of calycanthaceous alkaloids have been reported (Hino & Yamada 1963; Hall et al. 1967; Fang et al. 1994; Movassaghi & Schmidt 2007; Ruiz-Sanchis et al. 2011; Li et al. 2012; Araki et al. 2013; Peng et al. 2013; Kim & Movassaghi 2015; Xu & Cheng 2015). However, little attention has been paid to the structural optimisation of the core structure tetrahydropyrroloindole of calycanthaceous alkaloids for their antimicrobial activities. Therefore, we envisioned that the structural optimisation might be a lead for the discovery of novel agricultural fungicides.

Herein, a series of N-protected tryptophan derivatives were synthesised using tryptophan as starting material via an efficient method. Their antimicrobial effects and structure antifungal activity relationships were investigated. To the best of our knowledge, the antimicrobial activities of the synthetic derivatives were reported for the first time.

2. Results and discussion

2.1. Synthesis

The synthetic route of the title compounds is outlined in Scheme 1. The N-protected tryptophan derivatives were synthesised using tryptophan as the starting material via alkylation at the 1-N position. Alkylation resulted in unexpected ring opening of the calycanthaceous alkaloids core structure at the C–N bond, and the possible mechanism of the unexpected ring opening of the calycanthaceous alkaloids core structure at the C–N bond is shown in Figure 2; 21 tryptophan methyl ester derivatives were synthesised, 19 of which have not been previously characterised. The synthesised compounds were characterised by ^{1}H NMR, ^{13}C NMR, DEPT (90° and 135°) and MS analysis.

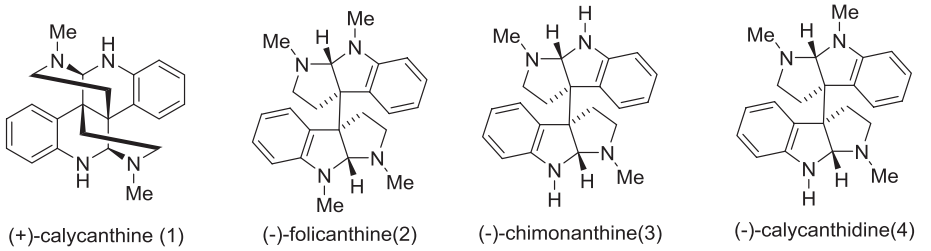


Figure 1. Structures of calycanthaceous alkaloids.

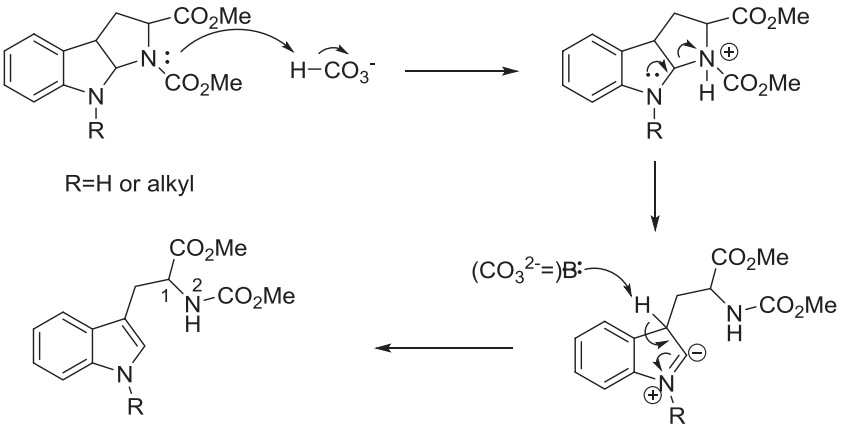


Figure 2. The possible mechanism of the unexpected ring opening of the calycanthaceous alkaloids core structure at the C–N bond.

2.2. Fungicidal activity

The biological activities of these compounds towards a wide variety of plant pathogen fungi were evaluated, with the following results:

Inhibitory effects of N-protected tryptophan derivatives against phytopathogenic fungus are listed in Table 1. Mycelium growth inhibition assay was utilised, with carbendazim as a positive control, to evaluate the biological activities of the 21 synthesised N-protected tryptophan derivatives against *Eggplant Verticillium* (*E. Verticillium*), *Fusarium oxysporum* (*F. oxysporum*), *Colletrotrichum gloesporioides*, *Botrytis cinerea* (*B. cinerea*), *Alternaria alternate* (*A. alternate*), *Gibberella zeae* (*G. zeae*), *Sclerotinia sclerotiorum* (*S. sclerotiorum*) and *Curvularia lunata* (*C. lunata*) at the concentration of 100 μg mL^{-1}. Among the synthesised compounds, compounds **a19** and **a21** displayed activity against *F. oxysporum*, and compound **a21** showed high activity against *F. oxysporum* and *E. Verticillium*, with EC_{50} values of 58.27 and 77.39 μg mL^{-1}, respectively(Tables 2 and 3).

3. Experimental

3.1. Instruments and chemicals

All reagents and solvents were of reagent grade or purified according to standard methods before use. Analytical thin-layer chromatography (TLC) was performed with silica gel plates using silica gel 60 GF_{254} (Qingdao Haiyang Chemical Co., Ltd.). Melting points were measured on an electrothermal digital apparatus made in Beijing and were uncorrected. The ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) were obtained on a Bruker AM-500 FT NMR spectrometer with $CDCl_3$ as the solvent and TMS as the internal standard. MS were recorded under ESI conditions using a Thermo LCQ Fleet instrument. Infrared spectra were measured on a Nicolet FT-IR-20SX instrument using a potassium bromide (KBr) disc, scanning from 625 to 4000 cm^{-1}. Optical rotation was measured by Rudolph Autopol II. Yields were not optimised. The title compounds were synthesised under a nitrogen atmosphere.

Table 1. Inhibitory effects of N-protected tryptophan derivatives against phytopathogenic fungus.

Compound	Inhibitory ratio under 100 μg mL^{-1} (mean ± SD) (%)							
	B. c.	*EV. d.*	*C. g.*	*F. o. n.*	*G. z.*	*A. a.*	*C. g.*	*S. s.*
a1	13.38 ± 0.88	4.37 ± 3.83	19.84 ± 1.47	14.14 ± 5.40	10.08 ± 1.96	16.73 ± 3.05	13.82 ± 3.72	34.87 ± 2.51
a2	23.14 ± 4.79	18.53 ± 4.32	17.32 ± 2.12	13.83 ± 2.20	21.44 ± 3.92	9.82 ± 3.16	23.82 ± 4.51	38.43 ± 1.13
a3	19.23 ± 4.12	23.31 ± 2.78	26.19 ± 4.51	18.56 ± 2.39	28.42 ± 2.26	13.67 ± 2.58	21.32 ± 5.25	37.21 ± 2.21
a4	15.34 ± 2.70	20.94 ± 6.43	18.33 ± 2.67	5.56 ± 2.21	23.95 ± 1.26	27.10 ± 2.61	–	32.18 ± 2.61
a5	21.67 ± 4.08	22.68 ± 3.67	19.38 ± 1.13	24.14 ± 2.61	21.37 ± 1.13	28.12 ± 2.12	10.91 ± 3.16	39.89 ± 2.84
a6	31.29 ± 4.17	27.32 ± 2.14	24.37 ± 3.40	19.32 ± 1.68	24.29 ± 1.29	26.67 ± 2.71	11.33 ± 3.05	34.45 ± 4.08
a7	17.38 ± 3.71	24.47 ± 4.37	18.48 ± 5.57	9.78 ± 1.92	22.02 ± 2.19	17.23 ± 1.62	9.09 ± 5.30	29.49 ± 4.17
a8	20.89 ± 5.38	31.81 ± 2.55	22.75 ± 2.94	10.74 ± 1.03	17.93 ± 3.70	28.31 ± 3.16	15.64 ± 3.99	29.31 ± 2.71
a9	22.54 ± 5.99	20.77 ± 7.29	21.76 ± 2.26	25.86 ± 4.12	25.40 ± 4.66	21.28 ± 2.58	15.27 ± 4.07	29.37 ± 2.20
a10	19.32 ± 6.28	12.26 ± 6.37	9.85 ± 2.06	8.17 ± 2.70	4.15 ± 1.29	17.40 ± 2.94	13.23 ± 3.10	34.13 ± 2.39
a11	28.15 ± 2.15	25.92 ± 3.28	20.93 ± 1.81	30.25 ± 4.08	9.30 ± 3.79	29.81±5.88	23.97 ± 2.77	41.46 ± 1.42
a12	23.89±4.24	16.23 ± 5.31	16.67 ± 1.27	20.79 ± 4.17	13.21 ± 2.26	28.71±3.83	21.01 ± 1.47	43.89±2.36
a13	19.33 ± 5.23	23.58 ± 4.23	28.29 ± 1.47	6.57 ± 5.38	28.95 ± 2.43	35.15 ± 1.05	21.66 ± 5.63	29.43 ± 1.92
a14	18.53 ± 3.61	24.66 ± 2.23	24.16 ± 2.12	7.58 ± 2.15	11.45±3.07	24.20 ± 2.12	6.58 ± 4.56	34.32 ± 2.90
a15	27.27 ± 1.29	21.60 ± 2.65	19.55 ± 2.58	16.98 ± 6.28	15.83 ± 4.29	27.71 ± 1.56	12.62 ± 1.81	41.92 ± 4.24
a16	29.43 ± 2.92	22.08 ± 4.66	13.63 ± 1.13	15.59 ± 3.71	19.62 ± 1.27	29.55 ± 1.81	22.18 ± 1.11	39.44 ± 2.20
a17	28.32 ± 3.56	21.10 ± 8.55	17.42 ± 4.51	9.41 ± 4.08	16.98 ± 3.65	38.06 ± 2.58	24.12 ± 2.58	42.75 ± 2.84
a18	24.53 ± 5.88	7.17 ± 2.55	7.58 ± 3.83	7.67 ± 2.70	20.75 ± 2.10	40.49 ± 5.57	16.34 ± 4.51	42.64 ± 2.70
a19	32.55 ± 2.62	4.56 ± 1.70	29.33 ± 1.27	45.68 ± 0.53	32.33 ± 2.46	33.25 ± 5.03	23.66 ± 3.83	45.06 ± 3.71
a20	19.65 ± 1.92	13.17 ± 1.61	20.39 ± 2.55	18.83 ± 5.59	19.67 ± 4.59	31.31 ± 1.70	27.44 ± 1.56	27.23 ± 0.88
a21	29.71 ± 4.57	54.52 ± 1.29	24.86 ± 2.61	56.23 ± 0.88	35.89 ± 1.53	29.72 ± 1.92	27.44 ± 2.61	48.19±1.06
Carbendazim	99.86 ± 1.02	100 ± 0.00	100 ± 0.00	100 ± 0.00	100 ± 0.00	100 ± 0.00	100 ± 0.00	100 ± 0.00

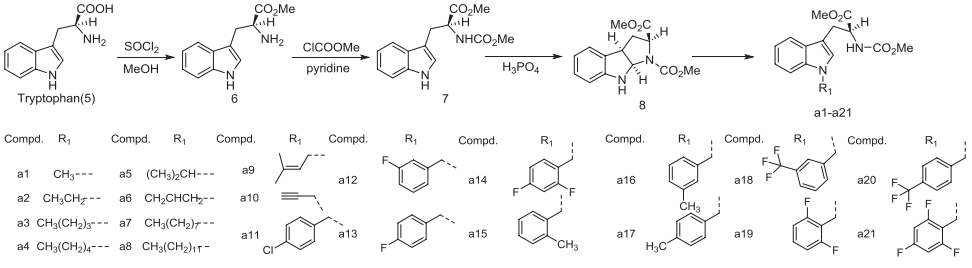
Note: The carbendazim was used as the positive control. *B. c.: Botrytis cinerea ： EV. d.: Eggplant Verticillium, C. g ： Colletotrichum gloesporioides, F. o. n.: Fusarium oxysporum (FON), G. z.: Gibberella zeae, A. a.: Alternaria alternate, C. g.: Curvularia lunata, S. s.: Sclerotinia sclerotiorum.*

Table 2. Inhibitory effect of **a21** against *F. oxysporum*.

	Fusarium oxysporum		
Compound	Regression equation	Correlation coefficient (r^2)	EC_{50} ± SD (μg mL^{-1})
a21	$Y = 0.3413X + 3.6126$	0.8395	58.27 ± 3.31

Table 3. Inhibitory effect of **a21** against *F. oxysporum* and *Eggplant Verticillium*.

	Fusarium oxysporum			*Eggplant Verticillium*		
Compound	Regression equation	Correlation coefficient (r^2)	EC_{50} ± SD (μg mL^{-1})	Regression equation	Correlation coefficient (r^2)	EC_{50} ± SD (μg mL^{-1})
a21	$Y = 0.3413X + 3.6126$	0.8395	58.27 ± 3.31	$Y = 0.5703X + 2.5501$	0.8470	77.39 ± 1.68



Scheme 1. Synthetic route for the title compounds **a1**-**a21.**

3.2. Synthesis

The general synthetic methods for compounds **a1**–**a21** are depicted in Scheme 1.

3.2.1. Synthesis of compound 6

To a stirred solution of tryptophan (4.08 g, 20 mmol) in 30 mL of methanol was added thionyl chloride (1.74 mL, 24 mmol, 1.2 eq.) dropwise at 0 °C. The resulting mixture was allowed to warm to RT for a further 1 h. The solvents were removed to provide the desired product **6**.

3.2.2. Synthesis of compound 7

To a solution of the compound **6** (3.27 g, 15 mmol) in 20 mL of pyridine was added methyl chloroformate (1.44 mL, 18 mmol, 1.2 eq.) dropwise at 0 °C. The resulting mixture was allowed to warm to RT until TLC monitoring indicated the disappearance of the material **6** (0.5 h), and then, the reaction mixture was quenched with methanol (1 mL) and extracted three times with ethyl acetate. The organic extracts were combined, washed with brine, dried over Na_2SO_4 and concentrated. Purification by flash chromatography on silica gel (petroleum ether: acetone = 4:1) afforded the compound **7**.

3.2.3. Synthesis of compound 8

To the compound **7** (2.77 g, 10 mmol) was added 27 mL of H_3PO_4 (85%), and the mixture was stirred until TLC monitoring indicated the disappearance of the material **7** (12 h). The reaction mixture was poured into ice water and neutralised to pH 7 with a saturated $NaHCO_3$

and extracted three times with ethyl acetate. The separated organic phase was washed with water and brine and dried over Na_2SO_4. The solvent was removed under reduced pressure. The crude product **8** was used for the next step without further purification.

3.2.4. General procedure for the preparation of compounds a1–a21

To a solution of the compound **8** (276 mg, 1 mmol) in acetonitrile (20 mL) was added $NaHCO_3$ (252 mg, 3 mmol, 3 eq.) and the corresponding desired reagents (b-series) (1.5 mmol, 1.5 eq.). The resulting mixture was refluxed for 12 h. and then extracted three times with dichloromethane. The organic extracts were combined, washed with brine, dried over Na_2SO_4 and concentrated. Purification by flash chromatography on silica gel afforded the compounds **a1**-**a21**.

Methyl N-(methoxycarbonyl)-1-methyl-L-tryptophanate(**a1**) (Taniguchi et al. 1983): Reagents: methyl iodide. colourless crystals, ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.29 (d, 2H, J = 5.1), 3.66 (s, 3H), 3.68 (s, 3H), 3.74 (s, 3H), 4.67 (d, 1H, J = 7.6), 5.23 (d, 1H, J = 6.8), 6.84 (s, 1H), 7.11 (t, 1H, J = 7.7), 7.22 (t, 1H, J = 7.7), 7.27 (t, 1H, J = 8.2), 7.52 (d, 1H, J = 7.9) ^{13}C NMR ($CDCl_3$, 125 MHz) δ 27.80 (CH_2), 32.72 (CH_3), 52.29 (CH_3), 52.33 (CH_3), 54.48 (CH), 108.24 (C), 109.32 (CH), 118.67 (CH), 119.19 (CH), 121.82 (CH), 127.46 (CH), 128.03 (C), 136.93 (C), 156.48 (C), 172.51 (C).

The data of the other compounds and the NMR spectral details can be found in the Supplementary data.

3.3. Biological assay

The antimicrobial activity of N-protected tryptophan derivatives was measured according to the previously reported method (Zhang, Li & Wu 2009; Zhang et al. 2013).

3.3.1. Inhibition of spore germination method

The spore suspension was adjusted with sterile distilled water. The compounds dissolved in 1% dimethyl sulfoxide (DMSO), and then, dilutions with the spore suspensions were made in a concentration of 100.0 μg mL^{-1}. A known volume of 70 μL of the spore suspensions was taken onto the glass slide. About 100 spores were counted, and percentage of spore germination was calculated. Carbendazim was used as the positive control and the blank test. All experiments were conducted in triplicate. EC_{50} was determined by performing the bioassay as described above with concentrations of 100, 75, 50, 37.5 and 25 μg mL^{-1}, respectively.

3.3.2. Inhibition of the growth of fungal mycelium

The tested pathogenic fungi: *E. Verticillium, F. oxysporum, Colletotrichum gloesporioides, B. cinerea, A. alternate, G. zeae, S. sclerotiorum* and *C. lunata* were provided by the Institute of Pesticides, Northwest A&F University. The tested compounds dissolved in 1% of DMSO were screened for antifungal activity *in vitro* by measurement of inhibitory zone diameter. The general procedure is as follows:

Cultures of the test fungus were maintained on potato-dextrose-agar medium and were subcultured in Petri dishes prior to testing. The ready-made medium was suspended in distilled water. Stock solutions were prepared by dissolving the test materials in sterile distilled water and diluted to a concentration of 100.0 μg mL^{-1}. The medium was poured into

a set of two Petri dishes (two replicates) under aseptic conditions in a laminar flow chamber. When the medium in the plates was partially solidified, a 5-mm-thick disc of fungus (spores and mycelium) cut from earlier subcultured Petri dishes was placed at the centre of the semi-solid medium and the lids of the dishes were replaced. The treated and control dishes were kept in an incubator at 26 (±2) °C till the fungal growth in the control dishes was almost complete (2 ± 3 days). The mycelial growth of fungus (mm) in both treated (T) and control (C). About 1% of DMSO and carbendazim were used as the negative control and the positive control, respectively. Petri dishes were measured diametrically in three different directions, and the growth inhibition (I) was calculated using the formula:

$$I(\%) = \{(C\text{-}d) - (T\text{-}d)\}/(C\text{-}d) \times 100$$

where d: diameter of the cut fungus, C: diameter of the control fungus, T: diameter of the treated fungus (measurement unit: mm, two colonies were counted in two dishes. It was repeated for three times.). EC_{50} was determined by performing the bioassay as described above with five different concentrations.

4. Conclusions

In conclusion, 21 N-protected tryptophan derivatives were synthesised by modification at the 1-N position, and evaluated for their antimicrobial activity against a wide variety of plant pathogen fungi. The bioassays indicated that among the synthesised compounds, the short-chain alkyl substituents at the 1-N position exhibited high degrees of activity against Bacillus subtilis, while the long-chain alkyl substituents at the 1-N position showed no activity. The analogues **a19** and **a21** demonstrated high degrees of activity against *F. oxysporum*, sharing fluorine substituents at 2, 6-position on the phenyl groups in common. On the basis of the SAR analysis, it can be concluded that the variances among substituents on the 1-N position showed a significant relationship with fungicidal activity against a wide variety of plant pathogen fungi. Furthermore, considering that the bioassay of the title compounds was evaluated, effects of the chain alkyl substituents may contribute to the significant variations in fungicidal potency. These results will pave the way for further design, structural modification and development of calycanthaceous alkaloids as antimicrobial agents.

Disclosure statement

No potential conflict of interest was reported by the authors.

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