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Synthesis and biological evaluations of a series of calycanthaceous analogues as antifungal agents

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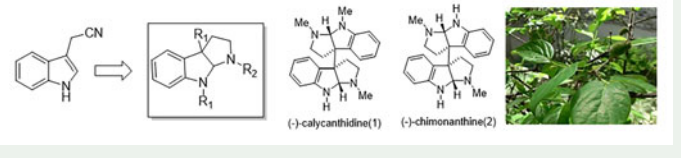
ABSTRACT

Starting from indole-3-acetonitrile, a total of 66 new calycanthaceous alkaloid analogues were synthesised in excellent yields. The prepared compounds were evaluated for their biological activities against a broad range of plant pathogen fungi. The results of bioassays indicated that the majority of tested compounds displayed comparable or better *in vitro* bioactivities than the positive control. Notably, Compound **a1** displayed a significant activities against *B. cereus*, *Escherichia sp* and *R. solanacearum*, even better than the positive control streptomycin and Penicillin, with the same MIC value of 15.63 μg mL^{-1}. Compound **a1** displayed a broad spectrum and remarkably activities among the tested calycanthaceous analogues and might be a novel potential leading compound for further development of antifungal agents. The results obtained in the study will be very helpful for further design and structural optimisation of calycanthaceous alkaloids as potential agrochemical lead for plant disease control.



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Calycanthaceous alkaloids; synthesis; plant pathogen fungi; biological activity; SAR

1. Introduction

Pesticides play a key role in our life, not only for crop protection in agriculture, but also for human health. The exploitation of new pesticides, especially the pesticides with high efficacy and selectivity against target species, has become an increasing

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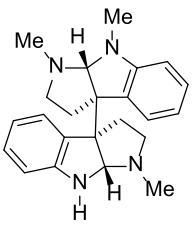
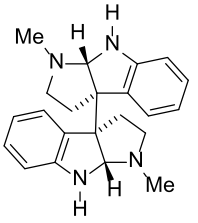


(-)-calycanthidine(1)



(-)-chimonanthine(2)

Figure 1. Structures of calycanthaceous alkaloids.

focus in agricultural chemistry. Imitating the chemistry of biologically active natural products is one approach for developing such pesticides (Du 2003; Huang et al. 2007).

The Calycanthaceae plants (Figure 1), mainly distributed in China, North America and Australia, are an important class of alkaloids that can be isolated from the roots, leaves, flowers, and fruits of *Chimonanthus praecox* (Bowman et al. 2005; De Fusco et al. 2017). Calycanthaceous alkaloids, which contain hexahydropyrroloindole skeletons, have been used as traditional chinese medicines for the treatment of fungal infection (Bowman et al. 2005), hypertension, tumour, inflammatory, and melanogenesis (Hino and Yamada 1963; Hall et al. 1967; Fang et al. 1994; Movassaghi and Schmidt 2007; Ruiz-Sanchis et al. 2011; Li et al. 2012; Araki et al. 2013; Peng et al. 2013; Kim and Movassaghi 2015; Xu and Cheng 2015).

Our group has recently reported the preparation and biological evaluations of a series of calycanthaceous analogues. We discovered that different substituents at N position could remarkably affect the biological activities. (Zheng et al. 2012, 2016a, 2016b, 2017, 2018a, 2018b). In addition, introducing Fluorine Substitutes into the natural product derivatives could enhance their biological activity (Jia et al. 2018). These findings inspired us to further modify the structure of calycanthaceous alkaloids with functional motifs so as to acquire potential agrochemical leads for plant disease control.

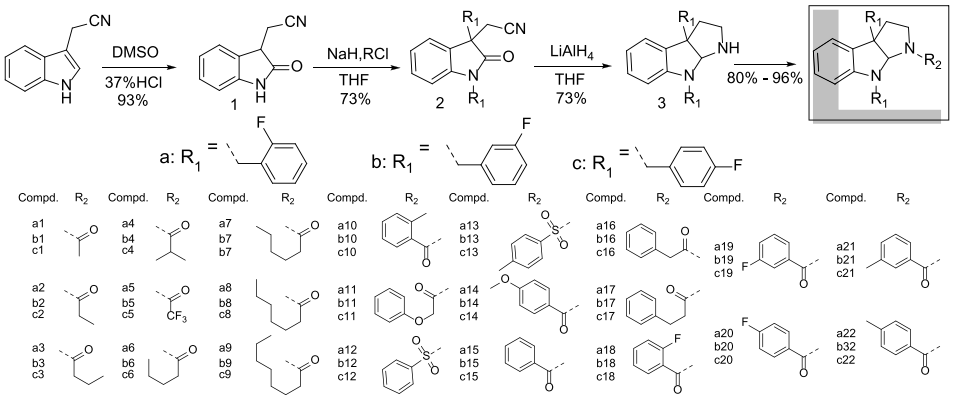
As a continuation of the development of new natural-product-based antifungal agents, a series of N-substituted calycanthaceous alkaloid analogues were designed and prepared, and their structures were characterised by ^{1}H NMR, ^{13}C NMR and MS.

To the best of our knowledge, the biological activities of the prepared analogues are reported for the first time.

2. Results and discussion

2.1. Design and synthesis of calycanthaceous alkaloids analogues

The synthetic route of title compounds is given in Scheme 1. The calycanthaceous alkaloid analogues were prepared according to a previously reported procedure in our group, and their spectral data were consistent with reported values (Zheng et al. 2016a, 2016b, 2017, 2018a, 2018b). The derivatives of calycanthaceous alkaloids were prepared from indole-3-acetonitrile via acylation at the N position. A total of 66 calycanthaceous analogues were prepared and characterised by ^{1}H-NMR, ^{13}C-NMR spectroscopy and ESI-MS.



Scheme 1. Synthetic route to the title compounds **a1–a22, b1–b22 and c1–c22**.

2.2. Antimicrobial activity

Inhibitory effects of calycanthaceous alkaloid analogues against a wide range of plant pathogen fungi are listed in Table 1. MIC were examined with Carbendazim, Amphotericin B, Chlorothalonil, Gentamicin, Streptomycin, Penicillin, and Fluconazole as the positive control, to evaluate the activities of the synthesised calycanthaceous alkaloid analogues against *Verticillium dahliae, Fusarium oxysperium sp. vasinfectum, Cytospora juglandis, Aspergillu sflavu, Penicillium citrinum, Fusarium oxysporum, Colletotrichum orbiculare, Aspergillus niger, B. cinerea Pers, Curvularia lunaia, Escherichia sp, Pseudomonas aeruginosa, Ralstonia solanacearum, Bacillus cereus, Staphylococcus aureus, Candida krusei, Crytococcus Neofonmans* and *Candida tropicalis.*

Antibacterial results are shown in Table 1. It is manifested that these series of analogues generally exhibit more effective antimicrobial activity than the positive control. Compound**a1** displayed better activity against *Escherichia sp* than that of streptomycin, with MIC value of 15.63 μg mL^{-1}. Compounds **b13** and **c13** illustrated much more effective activities against *V. dahliae* than the positive control Chlorothalonil, with MIC value of 31.25 μg mL^{-1}. Compound **c13** showed improved activity compared with the positive control Chlorothalonil against *V. dahliae*, with MIC value of 31.25 μg mL^{-1}. The activity of Compound **a17** is more potent than carbendazol, amphotericin B and Chlorothalonil against *F. oxysporum f. sp.*, with MIC value of 31.25 μg mL^{-1}. Compound **c2** illustrated better activity against *C. juglandis* than the positive control carbendazol, with MIC value of 31.25 μg mL^{-1}. Compound **c2** illustrated much more effective activity against *C. juglandis* than that of amphotericin B and Chlorothalonil, with the same MIC value of 31.25 μg mL^{-1}. Compound **b8** revealed better activity against *C. orbiculare* than the positive control amphotericin B and Chlorothalonil, with the same MIC value of 31.25 μg mL^{-1}. Compounds **a8** and **a13** manifested improved activity compared with the positive control carbendazol, amphotericin B and Chlorothalonil against *F. oxysporum f. sp.*, with the same MIC value of 62.5 μg mL^{-1}. Compound **a2** illustrated much more active against *A. niger* than that of carbendazol, with MIC value of 62.5 μg mL^{-1}. Compounds **a3**, **a8**, **b1**, **b7**, **b17**, **b18**, **c3** and **c8** showed better activities against *C. juglandis* than the positive control amphotericin B, with the same MIC value of 62.50 μg mL^{-1}. Compounds **b3** and **b4** illustrated better activity than the control Chlorothalonil against *F. oxysporum f. sp.*, with the

Table 1. MIC of compounds against plant pathogenic fungi, gram-negative bacteria, ram-positive bacteria and human pathogenic fungi

plant pathogen fungi											gram-negative bacteria			*gram-positive bacteria*		*human pathogenic fungi*		
Comp.	*V.d*	*F.o*	*C.j*	*A.s*	*P.c*	*F.o*	*C.o*	*A.n*	*B.c.*	*C.l*	*E.s*	*P.a*	*R.s*	*B.c*	*S.a*	*C.k*	*C.N*	*C.t*
MIC (μg/ml)																		
a1	125	—	125	250	250	125	250	125	—	125	15.63	—	—	15.6	15.6	250	—	250
a2	250	—	125	250	250	250	250	62.5	—	250	250	—	—	31.3	—	250	—	250
a3	125	—	62.5	250	250	125	250	125	—	—	250	250	250	250	250	250	—	250
a4	250	—	125	250	—	125	250	250	—	250	—	—	250	31.3	125	125	—	250
a5	250	—	250	250	—	125	250	250	—	250	—	—	—	—	—	250	—	125
a6	62.5	250	250	250	125	125	—	250	—	—	250	250	250	250	250	250	—	125
a7	62.5	—	250	250	125	125	250	250	—	250	—	125	250	—	—	250	—	—
a8	62.5	250	62.5	250	250	250	250	250	—	125	—	250	125	250	—	250	—	—
a9	125	—	—	250	250	250	—	250	—	—	—	—	—	—	—	250	—	250
a10	—	—	250	250	250	125	—	125	—	—	—	—	—	—	—	250	—	250
a11	250	—	250	250	62.5	250	—	250	—	—	—	—	—	—	—	—	—	—
a12	62.5	250	250	250	250	250	250	250	—	—	—	—	—	125	250	250	—	—
a13	250	250	250	250	—	250	250	250	—	—	—	—	—	125	—	250	—	250
a14	250	—	250	250	250	250	—	250	—	—	—	—	—	—	—	125	—	125
a15	125	—	250	250	—	250	—	250	—	—	250	62.5	125	250	250	250	250	125
a16	125	250	250	250	250	250	—	250	—	—	—	—	—	—	—	—	—	—
a17	—	31.3	125	250	250	250	250	250	—	—	—	—	—	—	—	250	—	—
a18	—	—	250	250	—	250	—	250	—	—	—	—	—	—	—	—	—	—
a19	—	—	125	250	250	250	—	250	—	—	—	—	—	—	—	250	—	—
a20	125	—	250	250	250	125	—	250	—	—	—	—	—	—	—	—	—	—
a21	—	—	125	250	250	250	—	250	—	—	—	250	125	—	—	—	—	—
a22	—	—	125	250	250	250	—	250	—	—	—	—	—	—	—	—	—	—
b1	62.5	—	62.5	250	—	250	—	250	—	—	—	—	250	250	—	—	—	—
b2	—	250	125	250	—	125	—	250	—	—	—	—	—	250	—	—	—	—
b3	—	125	125	250	—	250	—	250	—	—	—	—	—	250	—	—	—	250
b4	—	125	250	250	—	250	—	250	—	—	—	—	—	250	—	—	—	250
b5	—	—	125	250	250	250	—	250	—	—	—	—	—	—	—	—	—	—
b6	62.5	—	125	250	125	250	—	250	—	—	250	125	125	250	125	—	—	—
b7	62.5	250	62.5	250	125	125	250	—	—	—	—	62.5	62.5	250	—	250	—	—
b8	62.5	62.5	250	250	62.5	125	125	250	—	250	250	125	31.3	62.5	250	250	250	250
b9	62.5	125	250	250	250	250	250	250	250	250	250	62.5	125	62.5	250	250	250	—
b10	—	—	250	250	250	250	250	250	—	—	—	—	—	—	—	—	—	—
b11	—	—	250	250	—	—	—	250	—	—	—	—	—	—	—	—	—	—
b12	62.5	125	125	250	—	250	250	125	250	—	250	62.5	—	—	250	—	—	250
b13	31.3	62.5	125	250	250	250	250	125	—	—	—	—	—	62.5	250	—	—	—
b14	—	—	250	250	250	—	—	250	—	—	—	—	—	—	—	—	—	—
b15	—	—	125	250	—	—	—	250	—	—	—	125	—	—	—	—	—	—

(*continued*)

Table 1. Continued.

plant pathogen fungi											gram-negative bacteria			*gram-positive bacteria*		*human pathogenic fungi*		
Comp.	*V.d*	*F.o*	*C.j*	*A.s*	*P.c*	*F.o*	*C.o*	*A.n*	*B.c.*	*C.l*	*E.s*	*P.a*	*R.s*	*B.c*	*S.a*	*C.k*	*C.N*	*C.t*
b16	—	—	125	250	—	—	—	250	—	—	—	—	—	—	—	—	—	—
b17	—	—	62.5	250	—	—	250	250	—	—	—	—	—	—	—	—	250	—
b18	—	—	62.5	250	—	—	—	250	—	—	—	—	—	—	—	—	—	—
b19	—	—	250	250	—	—	—	250	—	—	—	—	—	—	—	—	—	—
b20	—	—	250	250	—	—	—	250	—	—	—	—	—	—	—	—	—	—
b21	—	—	250	250	250	—	—	250	—	—	—	250	—	—	—	—	—	—
b22	—	—	250	250	250	—	—	250	—	—	—	—	—	—	—	—	—	—
c1	250	—	—	250	—	250	250	250	—	250	—	—	—	—	—	—	—	—
c2	250	—	31.3	250	250	250	250	125	—	125	62.5	—	—	31.3	62.5	250	—	250
c3	250	—	62.5	250	250	125	250	125	—	—	250	—	—	—	—	250	—	250
c4	250	—	125	250	250	125	250	125	—	—	250	—	—	62.5	—	250	—	250
c5	250	—	250	250	—	—	250	250	—	250	—	—	—	—	—	250	—	250
c6	31.3	250	250	250	250	125	—	250	—	—	—	—	250	—	—	250	—	—
c7	62.5	250	125	250	250	125	250	250	—	250	—	125	250	250	—	250	—	—
c8	62.5	250	62.5	250	250	125	250	250	—	125	250	125	—	—	—	125	—	250
c9	125	—	—	250	250	250	—	250	—	—	—	—	—	—	—	250	—	—
C10	250	—	250	250	125	250	—	125	—	—	—	—	—	—	—	250	—	—
c11	—	—	250	250	250	250	—	250	—	—	—	—	—	—	—	250	—	—
c12	62.5	250	250	250	—	125	250	250	—	—	—	—	—	—	250	62.5	250	125
c13	31.3	125	250	250	—	250	250	250	250	—	—	125	—	125	250	250	—	250
c14	250	—	250	250	250	250	—	250	—	—	—	—	—	—	—	250	—	—
c15	125	—	250	250	—	250	—	250	—	—	—	—	—	—	—	—	—	—
c16	125	125	250	250	—	125	250	250	—	250	—	250	—	—	—	—	—	—
c17	31.3	125	125	250	—	125	250	250	—	—	—	—	—	—	—	—	—	—
c18	—	—	250	250	—	250	—	250	—	—	—	—	—	—	—	250	—	—
c19	125	—	250	250	250	250	—	250	—	—	—	—	—	—	—	250	—	—
c20	250	—	125	250	—	250	—	250	—	—	—	—	—	—	—	250	—	—
c21	—	—	250	250	—	250	—	250	—	—	—	—	—	—	—	—	—	—
c22	—	—	125	250	250	250	—	250	—	—	—	—	—	125	—	—	—	—
Ca	7.8	62.5	31.3	7.8	1.9	125	125	—	1.9	250						250	—	250
A	1.9	—	250	31.3	31.3	62.5	250	3.9	—	7.8						250	1.9	—
Ch	31.3	250	62.5	7.8	15.6	62.5	250	15.6	31.3	125						7.8	—	1.9
G											1.9	1.9	62.5					
S											31.3	—	250					
P														7.8	15.6			
F																62.5	—	250

Note: The Carbendazim, Amphotericin B, Chlorothalonil, Gentamicin, Streptomycin, Penicillin and Fluconazole were used as the positive controls; "–" means no inhibition effect. MIC: Minimal Inhibitory Concentration; *V.d.: V.dahliae; F.v.: F.oxysperium sp. Vasinfectum; C.j.: C. juglandis; A.s.: A.sflavu; P.c.: P.citrinum; F.o.: F. oxysporum; C.o.: C.orbiculare; A.n.: A.niger; B.c.: B. cinerea; C.l.: C.lunaia; E.s.: Escherichia sp; P.a.: P.aeruginosa; R.s.: R.solanacearum; B.c.: B.cereus; S.a.: S.aureus; C.k:C. krolimus; C.N.:C. Neofonmans; C.t.: C. tropicalis; Ca: Carbendazim; A:Amphotericin B; Ch: Chlorothalonil; G: Gentamicin; S: Streptomycin; P: Penicillin: F:Fluconazole.*

same MIC value of 125 μg mL^{-1}. Compounds **a1**, **a2**, **a4**, **a17**, **a19**, **a21**, **a22**, **b2**, **b3**, **b5**, **b6**, **b12**, **b13**, **b15**, **b16**, **c4**, **c7**, **c17** and **c20** revealed better activities against *C. juglandis* than that of amphotericin B, with the same MIC value of 125 μg mL^{-1}. Compounds **a1**, **a3**, **a10**, **b12** and **b13** illustrated much more activities against *A. niger* than that of carbendazol, with the same MIC value of 125 μg mL^{-1}. Compounds **a1, a8, c2** and **c8** manifested better activities against *C. hmaia* than that of carbendazol, with the same MIC value of 125 μg mL^{-1}.

Compounds **a1**, **a2**, **a3** and **c3** illustrated better activities against *B. cereus*, with MIC values of 15.63 μg mL^{-1}, 31.25 μg mL^{-1}, 31.25 μg mL^{-1} and 31.25 μg mL^{-1}, respectively. Compound **b8** manifested much more effective activity against *R. solanacearum* than the positive control gentamicin and streptomycin, with MIC value of 31.25 μg mL^{-1}. Compound **b7** illustrated better activity against *R. solanacearum* than the positive control streptomycin, with MIC value of 62.5 μg mL^{-1}. Compounds **a8**, **a15**, **b1**, **b6** and **b9** displayed improved activity compared with the positive control streptomycin against *R. solanacearum*, with MIC value of 125 μg mL^{-1}.

Compound **c12** illustrated better activity against *C. krolimus* than that of Fluconazole, with MIC value of 62.5 μg mL^{-1}. Compounds **a4** and **a14** manifested much more effective activities against *C. krolimus* than that of carbendazol and amphotericin B, with MIC value of 125 μg mL^{-1}. Compounds **a5**, **a6**, **a14** and **a15** revealed better activities against *C. tropicalis*, with MIC value of 125 μg mL^{-1}.

Compounds **b2** and **b13** showed moderate activities against *F. oxysperium sp. vasinfectum* to that of carbendazol, with MIC value of 62.5 μg mL^{-1}. Compounds **a3**, **a8**, **b1**, **b7**, **b17**, **b18**, **c3** and **c8** manifested comparable control efficacy against *C. juglandis* than that of Chlorothalonil, with MIC value of 62.5 μg mL^{-1}. Compounds **b2** and **b13** showed moderate activities against *F. oxysperium sp. vasinfectum* to that of carbendazol, with MIC value of 62.5 μg mL^{-1}. Compounds **a1**, **a3**, **a4**, **a5**, **a6**, **a7**, **a10**, **a20**, **b2**, **b7** and **b8** displayed comparable control efficacy against *F. oxysporum* than that of carbendazol, with MIC value of 125 μg mL^{-1}. Compound **b8** illustrated comparable control efficacy against *C. orbiculare* than that of carbendazol, with MIC value of 125 μg mL^{-1}. Compounds **a1**, **a8**, **c2** and **c8** displayed comparable control efficacy against *C. lunaia* than that of Chlorothalonil, with MIC value of 125 μg mL^{-1}.

Compound **a1** revealed comparable control efficacy against *R. solanacearum* than that of Penicillin, with MIC value of 15.63 μg mL^{-1}. Compound **b8** illustrated comparable control efficacy against *R. solanacearum* than that of gentamicin, with MIC value of 62.5 μg mL^{-1}.

3. Experimental

3.1. Instruments and chemicals

All reagents and solvents were 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., Qingdao, China). Melting points were measured on an Electrothermal digital apparatus (Beijing, China) and were uncorrected. The $^{1}H-NMR$ (500 MHz), and $^{13}C-NMR$ (125 MHz) were obtained on an AM − 500 FT − NMR spectrometer (Bruker Corporation, Switzerland) with $CDCl_3$ as the solvent and TMS as the internal standard. MS were recorded under ESI conditions using a

LCQ Fleet instrument (Thermo Fisher, Waltham, MA, USA). Yields were not optimised. The title compounds were synthesised under a nitrogen atmosphere.

3.2. Synthesis

3.2.1. Synthesis of intermediates 1-3

Intermediates **1-3** were synthesised according to our previously reported procedure (Zheng et al. 2016b).

3.2.2. Synthesis of compounds a1–a22, b1–b22 and c1–c22

Compound **3** was dissolved in pyridine (10 mL), then, the corresponding desired reagent was added at 0 °C. After refluxing for 2 h. The mixture was warmed to room temperature. Then, the resulting mixture was reacted for 1.5 h. At last, the resulting mixture was quenched with methanol (2 mL), and extracted 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 afforded the compounds **a1**–**a21** in yields from 80% to 96% (Characterization data see Supplementary materials).

3.3. Biological activity

The antimicrobial activity of calycanthaceous alkaloids analogues were measured according to the previously reported method (Zhang et al. 2009, 2013).

The tested compounds dissolved in 5% dimethyl sulfoxide (DMSO), to a concentration of 1.02 mg/mL, 100 μL of the solutions were added to the first well and serially diluted from first well by taking 100 μL into second. This two-fold dilution was continued down the plate and 100 μL from the 8th column of the plated discarded. The 9th column of the plate was reserved for negative control wells (without inocula) and the 10^{th} column, for the positive growth control wells (without antibacterial agent). The antibacterial concentrations were 256, 128, 64, 32, 16, 8, 4 and 2 μg/mL, respectively. The antibacterial test plates were incubated aerobically at 37 °C for 24 h, the antifungal test plates were incubated aerobically at 28 °C for 48 h. The MICs, MBC and MFC were examined. MBC and MFC were determined by plating 10 μL from each negative well and from the positive growth control on LB Agar and Sabouraud Dextrose Agar. MBC and MFC were defined as the lowest concentration yielding negative subcultures or only on colony. All tests were performed in triplicate and repeated if the results differed.

4. Conclusions

A total of 66 novel tetrahydropyrroloindole-based calycanthaceous alkaloid analogues were prepared using indole-3-acetonitrile as the starting material via acylation at the N3 position, and their activities against a wide range of plant pathogen fungi were screened. The results of bioassays revealed that most of the title compounds manifested potent activities against a broad variety of plant pathogen fungi, which were more effective than the positive controls. Notably, Compound **a1** displayed a significant activities against *B. cereus*, *Escherichia sp* and *R. solanacearum,* even better than

the positive control streptomycin and Penicillin, with the same MIC value of 15.63 μg mL^{-1}. Compound **a1** displayed a broad spectrum and remarkably high activities among the tested calycanthaceous analogues and might be a novel potential leading compound for further development of antifungal agents. The results obtained in the study will be very helpful for further design, structural optimisation, and development of calycanthaceous alkaloids as antimicrobial agents.

Disclosure statement

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