

Article

Synthesis and Investigation of Tetrahydro- β -carboline Derivatives as Inhibitors of Plant Pathogenic Fungi

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Abstract: A series of tetrahydro- β -carbolines substituted with an alkyl or acyl side chain was synthesized and screened for its antifungal activity against plant pathogenic fungi (*Bipolaris oryzae*, *Curvularia lunata*, *Fusarium semitectum*, and *Fusarium fujikuroi*). The structure activity relationship revealed that the substituent at the piperidine nitrogen plays an important role for increasing antifungal activities. In this series, 2-octyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (**3g**) displayed potent antifungal activities with a minimum inhibitory concentration of 0.1 $\mu\text{g}/\text{mL}$, including good inhibitory activity to the radial growth of fungus at a concentration of 100 $\mu\text{g}/\text{mL}$ compared to amphotericin B.

Keywords: tetrahydro- β -carbolines (TH β Cs); plant pathogenic fungi; radial growth; *N*-substituted TH β Cs



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1. Introduction

Plant pathogenic fungi are a major cause of plant diseases and pose enormous problems for agriculture worldwide. To control and curb their spread, many natural and synthetic pesticides have been applied as preventive and therapeutic usages and are crucial for the reliable production of crops. However, a long-standing use of fungicides can lead to the plant pathogens resistance. The prime focus of the agriculture sector is to develop potent fungicides to combat plant pathogenic fungi, which are growing at an alarming pace with a limited choice of available fungicides. Hence, modification of fungicides to improve the antifungal potential is a pressing need in modern agriculture.

Naturally occurring compounds have always played an important role in drug discovery. In particular, the β -carboline based moiety represents the core structure of several pharmaceutical activities [1–12], such as anticancer [3,4,13], antimicrobial [5], antimalarial [7], antiviral [9], and antifungal activities [14–20]. Many bioactive β -carboline-based compounds have been found to be important sources of drugs and drug leads, and most of them have been isolated from marine invertebrates, such as the marine sponge [5–8,10,21–23], tunicate [4,24,25], gorgonian [26] and alga [27]. For example, as shown in Figure 1, Eudistomins and their analogs were isolated from several species of marine organisms, mainly the active Caribbean colonial tunicate, and possessed a wide range of biological activities [28–32]. Ingenines, β -carboline alkaloids with a saturated/unsaturated tricyclic ring system, were isolated from the Indonesian marine sponge *Acanthostrongylophora ingens* and exhibited promising candidates for potent cytotoxic agents [13,33,34]. 6-Chloro-9-(3-(4-chlorophenoxy)propyl)-2,3,4,9-tetrahydro-1*H*-pyrido [3,4-*b*]indole TFA displayed in vitro and in vivo antifungal activity of *Cryptococcus neoformans* by induction of cell growth at the G2 phase on the Cdc25c/CDK1/cyclin B pathway [18]. Moreover, TH β C with an eight-carbon linear chain at the C1 position, (1*R*,3*S*)-methyl 1-octyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate, showed in vitro antifungal activity against *Candida*

glabrata with disruption of the membranes of fungal cells by increased asymmetry and decomposition of the cell surface [20]. Thus, the pharmaceutically important β -carboline-based natural products are advantageous for medicinal and organic research, while 1,3-disubstituted TH β Cs are reported to be synthetically and biologically interesting analogs [35]. Currently, Tadalafil, the hydantoin fused at the nitrogen and C3 of TH β C with a substituent at C1 is clinically used to treatment erectile dysfunction under the brand name Cialis [36] and is also used for pulmonary arterial hypertension treatment under the brand name Adcirca [37]. In our on-going search for novel compounds as inhibitors of plant pathogenic fungi, we are interested in C1 substituted TH β Cs as the skeleton, which is a common feature in many natural and synthetic compounds. Furthermore, investigations have indicated that nitrogen substituted with a longer alkyl or acyl side chain was an essential framework in various antifungal agents [38–43].

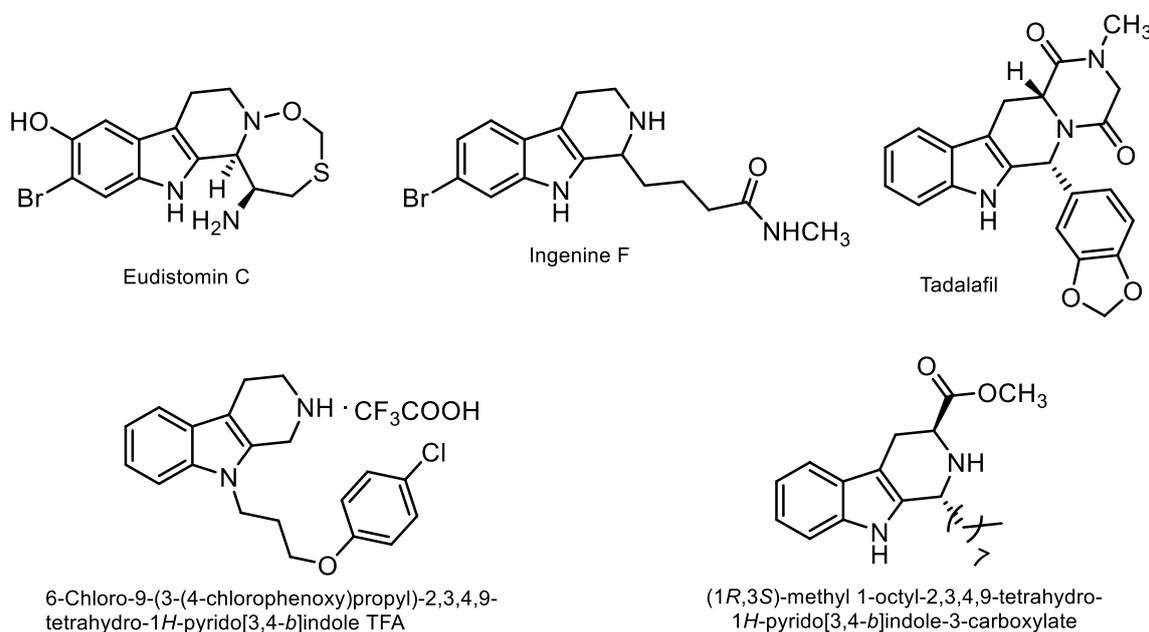


Figure 1. Chemical structures of the bioactive β -carboline analogues.

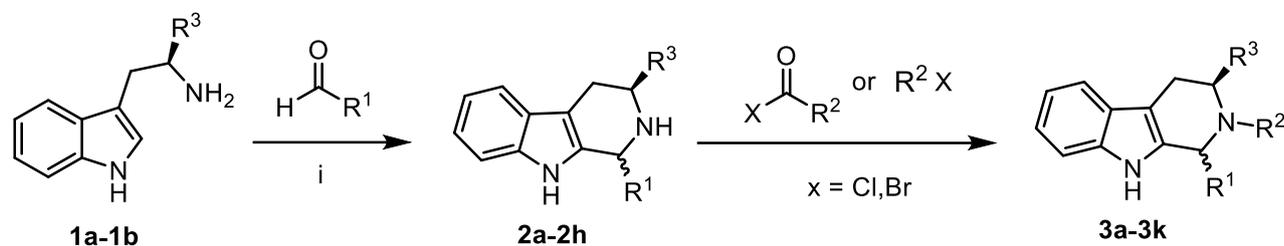
Thus, in this study, a series of *N*-substituted TH β Cs with an alkyl or acyl substituent together with C1 and/or C3 substituted TH β Cs was designed and synthesized from tryptamine and various aldehydes via the Pictet-Spengler reaction. *N*-substitutions of TH β Cs were prepared to evaluate their inhibition of four plant pathogenic fungi (*Bipolaris oryzae*, *Curvularia lunata*, *Fusarium semitectum*, and *Fusarium fujikuroi*).

2. Results and Discussion

2.1. Chemistry

The incorporation of aromatic substituents at the C1 position was reported to improve the activity, and the presence of the carbonyl group at the C3 position was also found to be important for the enhancement of activity [1,11,21,27,35]. Thus, we designed the preparation of the substituted TH β Cs via the efficient Pictet-Spengler reaction with tryptamine (**1a**), *L*-tryptophan methyl ester (**1b**), and appropriate aldehydes in acid media (Scheme 1). The TH β Cs (**2a–2h**) were obtained in poor to moderate yields. The steric hindrance and the presence of the electron-donating group at *ortho* position on the aromatic ring reduced the electrophilicity of aldehydes [44] and affected the yield of the TH β C ring, while the less hindered electron donating group induced the cyclization to the TH β C skeleton. The methyl ester substituent also increased the cyclization process. Next, the N2-substituted-TH β C bearing an alkyl or acyl side chain (**3a–3k**) was prepared from an acyl halide or alkyl halide in the presence of NEt_3 as a base. *N*-alkylated and *N*-acylated products were achieved

in moderated to high yields with the exception of 2-furoyl substituent (**3e**). The brown oil of compound (**3e**) was obtained in low yield due to the difficulty of purification. All synthesized compounds were characterized via MS, $^1\text{H-NMR}$, and $^{13}\text{C-NMR}$. All obtained TH β Cs were the racemic mixture at C1 and were used for antifungal evaluation.



Compounds	R ¹	R ²	R ³	Yields (%)
2a	H	-	H	53
2b	Phenyl	-	H	25
2c	2,5-Dimethoxyphenyl	-	H	9
2d	3-Methoxyphenyl	-	H	73
2e	2-Methoxyphenyl	-	H	9
2f	Ethylphenyl	-	H	47
2g	H	-	COOMe	69
2h	Phenyl	-	COOMe	80
3a	H	Acetyl	H	42
3b	H	Propionyl	H	78
3c	H	Octanoyl	H	41
3d	H	Benzoyl	H	61
3e	H	2-Furoyl	H	13
3f	H	Pentyl	H	57
3g	H	Octyl	H	42
3h	H	Crotyl	H	24
3i	H	Benzyl	H	29
3j	Phenyl	Acetyl	H	53
3k	Phenyl	Octyl	H	93

Scheme 1. Reagents and conditions: (i) RCHO, AcOH: dry CH₂Cl₂ (5:10), 80 °C, 1–2 h then basified to pH 9–10 using NH₄OH; (ii) NEt₃, CH₂Cl₂, rt 24 h.

2.2. Antifungal Activity

All TH β C derivatives were evaluated for their antifungal activity against four phytopathogenic fungi of rice, *Bipolaris oryzae*, *Curvularia lunata*, *Fusarium semitectum*, and *Fusarium fujikuroi*, using the results presented in Table 1. Amphotericin B and solvent were used as a positive and negative control, respectively. Most of the tested compounds showed activities for inhibition of *B. oryzae* and *C. Lunata*, while most of N-substituted TH β Cs were active against all tested fungi. The aromatic substituents at C1 of TH β Cs (**2b–2f**) showed a moderate activity against *B. oryzae* and *C. lunata* (zone of inhibition = 0.10–0.60 cm), whereas C1, C3-disubstituted TH β Cs (**2h**) showed a slight increase in inhibitory activity compared to that of C1-substituted TH β C (**2b**). The substituent at N2 of TH β Cs (**3a–3k**) was investigated. The linear acyl chains varying in length from 2 to 8 carbons (C2–C8), compounds (**3a–3c**), possessed no inhibitory activity. In contrast, the aromatic acyl groups (**3d–3e**) and alkyl chain substituents (**3f–3i**) led to increased activity with a zone of inhibition value of 0.10–0.60 cm. Thus, this preliminary in vitro antifungal activity indicated

that substituent at N2 position with aromatic acyl groups and alkyl chains was found to be helpful for the board spectrum antifungal activity. Therefore, the minimum inhibitory concentration (MIC) was determined for *N*-substituted TH β Cs (**3a–3k**). The MIC values of compounds (**3d–3i**) were 28–520 μ g/mL against *B. oryzae* and *C. lunata*. Interestingly, the *N*-octyl derivative (**3g**) showed the highest activity against *B. oryzae* (MIC = 28 μ g/mL), whereas the C1-phenyl and *N*-octyl derivative (**3k**) was less active than (**3g**) against *B. oryzae*, *C. lunata*, and *F. semitectum*. It can be indicated that racemic mixture of phenyl substituent at C1 was not favorable for the fungicidal activity and *N*-substituted TH β Cs play an essential role in antifungal activity. However, further studies of the enantiopure form of the C1 and *N*-substituted TH β Cs were under investigation.

Table 1. In vitro zones of inhibition (cm) and minimum inhibitory concentrations (μ g/mL) of the TH β C derivatives on phytopathogenic fungi.

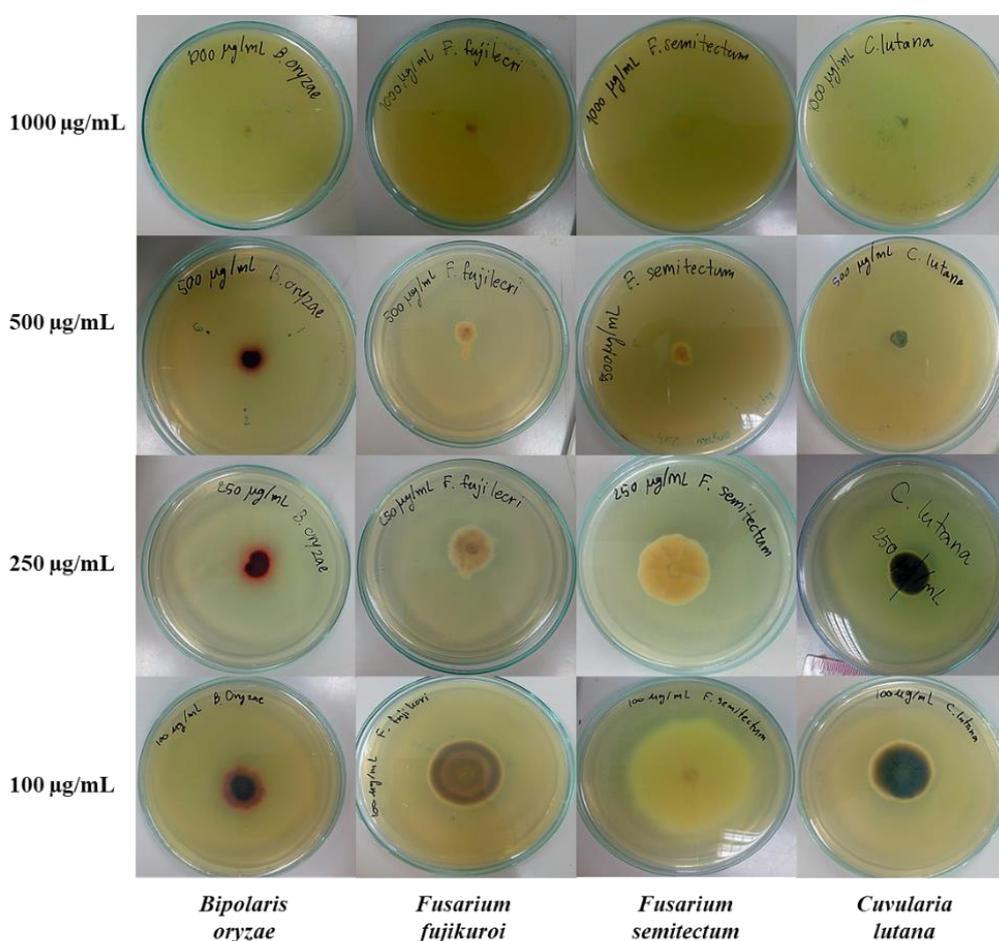
Compounds	<i>B. oryzae</i>		<i>F. fujikuroi</i>		<i>F. semitectum</i>		<i>C. lunata</i>	
	Zone of Inhibition	MIC ¹	Zone of Inhibition	MIC	Zone of Inhibition	MIC	Zone of Inhibition	MIC
2a	0.00	NT ²	0.00	NT	0.00	NT	0.00	NT
2b	0.00	NT	0.00	NT	0.00	NT	0.10 \pm 0.0	NT
2c	0.10 \pm 0.1	NT	0.00	NT	0.00	NT	0.00	NT
2d	0.60 \pm 0.1	NT	0.00	NT	0.00	NT	0.00	NT
2e	0.25 \pm 0.3	NT	0.00	NT	0.00	NT	0.40 \pm 0.0	NT
2f	0.40 \pm 0.0	NT	0.10 \pm 0.0	NT	0.00	NT	0.20 \pm 0.0	NT
2g	0.00	NT	0.00	NT	0.00	NT	0.00	NT
2h	0.15 \pm 0.1	NT	0.00	NT	0.00	NT	0.20 \pm 0.1	NT
3a	0.00	NT	0.00	NT	0.10 \pm 0.0	870 \pm 0.0	0.00	NT
3b	0.00	NT	0.00	NT	0.00	NT	0.00	NT
3c	0.00	NT	0.00	NT	0.00	NT	0.00	NT
3d	0.30 \pm 0.1	200 \pm 0.1	0.1 \pm 0.0	>512	0.20 \pm 0.0	>512	0.30 \pm 0.0	>512
3e	0.60 \pm 0.0	400 \pm 0.0	0.20 \pm 0.1	>512	0.25 \pm 0.1	>512	0.25 \pm 0.2	250 \pm 0.0
3f	0.10 \pm 0.0	110 \pm 0.0	0.00	NT	0.00	NT	0.00	NT
3g	0.10 \pm 0.0	28 \pm 0.0	0.1 \pm 0.0	>512	0.1 \pm 0.1	>512	0.15 \pm 0.1	200 \pm 0.0
3h	0.10 \pm 0.0	220 \pm 0.1	0.00	NT	0.00	NT	0.00	NT
3i	0.00	NT	0.00	NT	0.00	NT	0.10 \pm 0.0	250 \pm 0.0
3j	0.00	NT	0.00	NT	0.20 \pm 0.1	>512	0.00	NT
3k	0.35 \pm 0.1	210 \pm 0.0	0.00	NT	0.20 \pm 0.0	1700 \pm 0.0	0.10 \pm 0.0	270 \pm 0.0
Amphotericin B	0.21 \pm 0.1	0.78 \pm 0.0	0.00	>512	0.13 \pm 0.1	>512	0.15 \pm 0.1	0.33 \pm 0.1

¹ MICs were determined at the lowest concentration for complete inhibition of fungal growth. Results are the average of three duplicates after 7 days of incubation at 30 \pm 2 $^{\circ}$ C. ² NT; not tested.

Inhibitory activity of the *N*-octyl derivative (**3g**) was studied against a diameter of a colony of phytopathogenic fungi at concentration ranges of 0, 100, 250, 500, and 1000 μ g/mL. The results in Table 2 and Figure 2 show that compound (**3g**) at concentration of 100 μ g/mL inhibited the fungal growth by 68.2%, 37.4%, and 40% of *B. oryzae*, *F. Fujikuroi*, and *C. lunata*, respectively. However, at this concentration, compound (**3g**) could not inhibit the growth of *F. Semitectum*. Although, *N*-octyl substituted TH β C displayed less active than the antifungal drug Amphotericin B. The chemical modification of *N*-alkyl TH β Cs will provide the novel chemical scaffolds for further structural optimization of phytopathogenic fungi in the future.

Table 2. Inhibition activity of 2-octyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (**3g**) against a diameter of a colony of phytopathogenic fungi.

Compound	Concentration (µg/mL)	Diameter of Colony (cm) of Tested Fungi			
		<i>B. oryzae</i>	<i>F. fujikuroi</i>	<i>F. semitectum</i>	<i>C. lutana</i>
None (control)	-	7.77 ± 0.15	5.48 ± 0.08	5.17 ± 0.23	5.00 ± 0.27
3g	1000	NG ¹ (100%)	NG (100%)	NG (100%)	NG (100%)
	500	0.85 ± 0.05 (89.1%)	1.30 ± 0.35 (76.3%)	0.90 ± 0.07 (82.6%)	0.90 ± 0.12 (82.0%)
	250	1.43 ± 0.11 (81.7%)	2.23 ± 0.08 (59.4%)	3.08 ± 0.04 (40.6%)	1.98 ± 0.11 (60.5%)
	100	2.48 ± 0.13 (68.2%)	3.43 ± 0.04 (37.4%)	5.90 ± 0.21 (-14.0%)	3.00 ± 0.07 (40%)
Amphotericin B	0.6	3.30 ± 0.14 (57.6%)	5.68 ± 0.04 (-3.7%)	2.45 ± 0.17 (52.7%)	4.03 ± 0.08 (19.5%)

¹ NG; no growth.**Figure 2.** Inhibitory activity of (**3g**) against a diameter of a colony of phytopathogenic fungi.

3. Materials and Methods

3.1. Chemistry

3.1.1. General Information

The melting points were determined on an SMP2 model melting point apparatus and were uncorrected. The ¹H and ¹³C spectra were recorded in a Bruker AVANCE 300 MHz nuclear magnetic resonance spectrometer with CDCl₃, CD₃OD, and (CD₃)₂SO as the solvent and TMS as the internal standard. The chemical shifts were presented in parts per million (ppm, δ), the coupling constants (J) were reported in hertz (Hz), and the signals were described as singlet (s), doublet (d), triplet (t), quartet (q), quintet (qui), broad

singlet (br s), doublet of doublet (dd), doublet of triplet (dt), triplet of doublet (td), doublet of doublet of doublet (ddd), doublet of doublet of triplet (ddt), triplet of doublet of doublet (tdd), and multiplet (m). HR-MS was performed using Bruker Daltonics. All compounds were monitored using a TLC silica gel 60 F254 aluminum sheet. Column chromatography was performed using silica gel 60 (0.063–0.200 mm) and visualized under UV light at 254 and 365 nm. All chemicals were purchased from commercial suppliers.

3.1.2. General Procedure for the Synthesis of 1-substituted-tetrahydro- β -carbolines (**2a–2h**)

Tryptamine (**1a**) or tryptophan methyl ester (**1b**) was dissolved in AcOH: dry CH_2Cl_2 (5:10 mL) in a round-bottom flask. Then, aldehyde (1.2 eq) was slowly added to the solution, and the solution was refluxed for 1–2 h. After completion, the reaction mixture was cooled to room temperature and basified to pH 9–10 using NH_4OH . Afterwards, the solution was extracted with CH_2Cl_2 , and the organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product was purified using column chromatography (silica gel, 15% MeOH: CH_2Cl_2).

2,3,4,9-Tetrahydro-1*H*-pyrido[3,4-*b*]indole (**2a**). The title compound was synthesized from (**1a**) (268 mg, 1.7 mmol) and *para*-formaldehyde (60 mg, 2.0 mmol) to afford (**2a**) (153 mg, 53%) as a yellow solid. m.p. 185.9–187.5 °C (lit. 109–221 °C) [15,45]; $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 2.75 (t, $J = 5.7$ Hz, 2H), 3.18 (t, $J = 5.7$ Hz, 2H), 4.01 (s, 2H), 7.09 (dt, $J = 1.1$, 7.1 Hz, 1H), 7.14 (dt, $J = 1.3$, 7.1 Hz, 1H), 7.29 (d, $J = 7.2$ Hz, 1H), 7.48 (d, $J = 7.2$ Hz, 1H), 7.86 (br s, 1H); $^{13}\text{C-NMR}$ (125 MHz, CDCl_3) [46] δ 22.5 (CH_2), 43.2 (CH_2), 43.9 (CH_2), 108.7 (C), 110.7 (CH), 117.9 (CH), 119.4 (CH), 121.5 (CH), 127.6 (C), 132.7 (C), 135.6 (C).

1-Phenyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (**2b**). The title compound was synthesized from (**1a**) (321 mg, 2.0 mmol) and benzaldehyde (0.24 mL, 2.4 mmol) to afford (**2b**) (124 mg, 25%) as a yellow solid. m.p. 162.9–164.7 °C (lit. 160–161 °C) [47]; $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 1.97 (br s, 1H), 2.78–3.00 (m, 1H), 3.07–3.18 (m, 1H), 3.37 (dt, $J = 3.9$, 12.5 Hz, 1H), 5.17 (s, 1H), 7.10 (dt, $J = 1.9$, 6.9 Hz, 1H), 7.14 (dt, $J = 1.9$, 6.9 Hz, 1H), 7.17–7.23 (m, 1H), 7.27–7.37 (m, 5H), 7.52–7.56 (m, 1H); $^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ 22.5 (CH_2), 42.9 (CH_2), 58.1 (CH), 110.2 (C), 110.8 (CH), 118.3 (CH), 119.4 (CH), 121.8 (CH), 127.4 (C), 128.2 (CH), 128.5 (2CH), 128.8 (2CH), 134.4 (C), 135.9 (C), 141.7 (C).

1-(2,5-Dimethoxyphenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (**2c**). The title compound was synthesized from (**1a**) (494 mg, 3.1 mmol) and 2,5-dimethoxybenzaldehyde (615 mg, 3.7 mmol) to afford (**2c**) (86 mg, 9% yield) as a yellow solid. m.p. 132.2–133.6 °C; $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 2.87–2.92 (m, 2H), 3.15–3.25 (m, 1H), 3.29–3.39 (m, 1H), 3.67 (s, 3H), 3.84 (s, 3H), 5.65 (s, 1H), 6.68 (d, $J = 2.9$ Hz, 1H), 6.80–6.93 (m, 2H), 7.10 (dt, $J = 1.4$, 7.1 Hz, 1H), 7.14 (dt, $J = 1.4$, 7.0 Hz, 1H), 7.22–7.24 (m, 1H), 7.52 (d, $J = 7.0$ Hz, 1H), 7.83 (br s, NH); $^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ 21.1 (CH_2), 21.4 (CH_2), 41.0 (CH_2), 51.3 (CH), 55.8 (CH_3), 56.1 (CH_3), 109.6 (C), 110.9 (CH), 111.9 (CH), 113.9 (CH), 116.1 (CH), 118.3 (CH), 119.5 (CH), 121.9 (CH), 127.0 (C), 128.5 (C), 136.0 (C), 151.5 (C), 153.7 (C), 175.9 (C); HREI-MS: calcd for $\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}_2$ $[\text{M}]^+$: 308.1525, found: 308.1527.

1-(3-Methoxyphenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (**2d**). The title compound was synthesized from (**1a**) (303 mg, 1.9 mmol) and 3-methoxybenzaldehyde (0.20 mL, 2.3 mmol) to afford (**2d**) (385 mg, 73% yield) as an orange solid. m.p. 150.8–153.8 °C (lit. 154–156 °C) [48]; $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 2.82–3.04 (m, 2H), 3.10–3.22 (m, 1H), 3.32–3.43 (m, 1H), 3.75 (s, 3H), 5.32 (s, 1H), 6.84–6.91 (d, $J = 3.9$ Hz, 3H), 7.11 (dt, $J = 1.5$, 7.0 Hz, 1H), 7.16 (dt, $J = 1.5$, 7.0 Hz, 1H), 7.22 (d, $J = 2.0$ Hz, 1H), 7.23–7.29 (m, 1H), 7.53 (dd, $J = 2.0$, 7.0 Hz, 1H), 7.80 (br s, NH); $^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ 21.3 (CH_2), 41.7 (CH_2), 55.3 (CH_3), 57.2 (CH), 109.8 (C), 111.0 (CH), 111.5 (CH), 114.2 (CH), 118.3 (CH), 119.6 (CH), 121.0 (CH), 122.1 (CH), 127.0 (C), 129.9 (CH), 132.3 (C), 136.1 (C), 140.9 (C), 160.1 (C); HRESI-MS: calcd for $\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}$ $[\text{M}+\text{H}]^+$: 279.1492, found: 279.1486.

1-(2-Methoxyphenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (**2e**). The title compound was synthesized from (**1a**) (141 mg, 0.9 mmol) and 2-methoxybenzaldehyde (144 mg, 1.1 mmol) to afford (**2e**) (22 mg, 9% yield) as an orange solid. m.p. 97.8–99.3 °C (lit. 95–96 °C) [49]; $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 2.28 (br s, 1H), 2.81 (d, $J = 4.9$ Hz, 2H), 3.00–3.11

(m, 1H), 3.16–3.28 (m, 1H), 3.85 (s, 3H), 5.57 (s, 1H), 6.83 (t, $J = 7.4$ Hz, 1H), 6.92 (d, $J = 8.2$ Hz, 1H), 6.98 (dd, $J = 1.4, 7.5$ Hz, 1H), 7.06–7.18 (m, 3H), 7.26 (dd, $J = 1.5, 15.6$ Hz, 1H), 7.50 (d, $J = 3.7$ Hz, 1H), 7.94 (s, NH); ^{13}C -NMR (75 MHz, CDCl_3) δ 22.4 (CH_2), 41.7 (CH_2), 50.9 (CH_3), 55.5 (CH), 110.2 (C), 110.7 (CH), 110.8 (CH), 118.0 (CH), 119.2 (CH), 120.6 (CH), 121.4 (CH), 127.3 (C), 129.0 (CH), 129.2 (CH), 129.7 (C), 134.1 (C), 135.8 (C), 157.2 (C).

1-Phenethyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (**2f**). The title compound was synthesized from (**1a**) (489 mg, 3.1 mmol) and 3-phenylpropanal (491 mg, 3.7 mmol) to afford (**2f**) (396 mg, 47% yield) as an orange oil. ^1H -NMR (300 MHz, CDCl_3) δ 1.89–2.04 (m, 1H), 2.05–2.20 (m, 1H), 2.68–2.76 (m, 2H), 2.76–2.92 (m, 2H), 2.96–3.08 (m, 1H), 3.33 (td, $J = 4.7, 12.8$ Hz, 1H), 4.06 (d, $J = 5.2$ Hz, 1H), 7.07 (dt, $J = 1.3, 7.1$ Hz, 1H), 7.12 (dt, $J = 1.3, 7.0$ Hz, 1H), 7.16–7.33 (m, 6H), 7.47 (d, $J = 7.0$ Hz, 1H), 7.74 (br s, NH); ^{13}C -NMR (75 MHz, CDCl_3) δ 22.7 (CH_2), 29.7 (CH_2), 36.7 (CH_2), 42.4 (CH_2), 52.2 (CH), 109.1 (C), 110.7 (CH), 118.0 (CH), 119.0 (CH), 121.5 (CH), 126.0 (CH), 127.5 (C), 128.4 (2CH), 128.5 (2CH), 135.6 (C), 135.9 (C), 141.9 (C). HRESI-MS: calcd for $\text{C}_{19}\text{H}_{20}\text{N}_2$ [$\text{M}+\text{H}$] $^+$: 277.1700, found: 277.1706.

Methyl 2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate (**2g**). The title compound was synthesized from (**1b**) (271 mg, 1.2 mmol) and *para*-formaldehyde (45 mg, 1.5 mmol) to afford (**2g**) (197 mg, 69% yield) as a yellow solid. m.p. 171.8–173.6 °C (lit. 187.2–188.8 °C [50]); ^1H -NMR (300 MHz, CDCl_3) δ 2.05 (br s, NH), 2.89 (tdd, $J = 1.5, 4.2, 15.2$ Hz, 1H), 3.14 (tdd, $J = 1.5, 4.2, 15.2$ Hz, 1H), 3.79 (s, 3H), 3.81–3.85 (m, 1H), 4.08–4.30 (m, 2H), 7.10 (dt, $J = 1.3, 7.0$ Hz, 1H), 7.15 (dt, $J = 1.3, 7.0$ Hz, 1H), 7.30 (d, $J = 8.0$ Hz, 1H), 7.48 (d, $J = 7.4$ Hz, 1H), 7.87 (br s, NH); ^{13}C -NMR (75 MHz, CDCl_3) δ 24.2 (CH_2), 40.7 (CH_2), 51.1 (CH_3), 54.7 (CH), 105.5 (C), 109.8 (CH), 116.6 (CH), 118.2 (CH), 120.5 (CH), 126.0 (C), 130.6 (C), 135.0 (C), 172.7 (C).

Mixture of methyl 1-phenyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate (**2h**). The title compound was synthesized from (**1b**) (199 mg, 9.1 mmol) and benzaldehyde (0.11 mL, 1.1 mmol) to afford (**2h**) (224 mg, 80% yield) as a brown oil. ^1H -NMR (300 MHz, CDCl_3) δ (*cis* isomer) 3.11 (ddt, $J = 1.2, 6.9, 8.1$ Hz, 1H), 3.26 (ddt, $J = 1.0, 5.3, 8.0$ Hz, 1H), 3.69 (s, 3H), 3.94 (t, $J = 6.6$ Hz, 1H), 5.23 (s, 1H), 7.04–7.10 (m, 2H), 7.11–7.19 (m, 1H), 7.20–7.27 (m, 4H), 7.49–7.94 (m, 1H), 7.65–7.76 (m, 1H); ^{13}C -NMR (75 MHz, CDCl_3) δ (*cis* isomer) 25.7 (CH_2), 52.1 (CH_3), 56.8 (CH), 58.6 (CH), 108.7 (C), 110.9 (CH), 118.1 (CH), 119.4 (CH), 121.8 (CH), 127.0 (C), 128.0 (CH), 128.4 (CH), 128.6 (2CH), 128.7 (CH), 134.6 (C), 136.1 (C), 140.7 (C), 173.2 (C); ^1H -NMR (300 MHz, CDCl_3) δ (*trans* isomer) 3.01 (ddd, $J = 2.6, 7.7, 15.1$ Hz, 1H), 3.23 (ddd, $J = 1.9, 4.3, 15.1$ Hz, 1H), 3.69 (s, 3H), 3.94 (t, $J = 6.6$ Hz, 1H), 5.11 (s, 1H), 7.04–7.10 (m, 2H), 7.11–7.19 (m, 1H), 7.27–7.45 (m, 4H), 7.49–7.94 (m, 1H), 7.82–7.97 (m, 1H); ^{13}C -NMR (75 MHz, CDCl_3) δ (*trans* isomer) 24.7 (CH_2), 52.1 (CH_3), 52.3 (CH), 54.8 (CH), 108.3 (C), 110.9 (CH), 118.1 (CH), 119.5 (CH), 121.8 (CH), 126.9 (C), 128.0 (CH), 128.4 (CH), 128.6 (2CH), 128.7 (CH), 133.1 (C), 136.1 (C), 141.9 (C), 174.0 (C).

3.1.3. General Procedure for Preparation of

2-substituted-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (**3a–3i**)

2,3,4,9-Tetrahydro-1*H*-pyrido[3,4-*b*]indole (**2a**) (1 eq) was dissolved in CH_2Cl_2 (1 mL/mmol), and then NEt_3 (3 eq) was added to the solution. An acid halide or acyl halide was slowly added to the solution mixture. After stirring at room temperature for 24 h, the product was extracted with CH_2Cl_2 , and the organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product was purified using column chromatography (silica gel, 5% MeOH: CH_2Cl_2).

2-Acetyl-1,2,3,4-tetrahydro- β -carboline (**3a**). The title compound was synthesized from (**2a**) (150 mg, 0.90 mmol) and acetyl bromide (0.13 mL, 1.8 mmol) to afford (**3a**) (79 mg, 42% yield) as a yellow solid. m.p. 217.2–218.3 °C (lit. 237–238 °C [51]); ^1H -NMR (300 MHz, MeOD) δ rotamers 1/3 (from the duplicated triplet signal (1H) at 3.83 and 3.92 ppm); ^1H -NMR (300 MHz, MeOD) δ (major rotamer) 2.23 (s, 3H), 2.84 (t, $J = 5.7$ Hz, 2H), 3.83 (t, $J = 5.7$ Hz, 2H), 4.75 (s, 2H), 6.98 (t, $J = 7.6$ Hz, 1H), 7.02–7.10 (m, 1H), 7.29 (dd, $J = 4.0, 7.9$ Hz, 1H), 7.40 (d, $J = 7.6$ Hz, 1H); δ (distinct peaks for minor rotamer) 2.20 (s, 3H), 2.76 (t, $J = 5.7$ Hz, 2H), 3.92 (t, $J = 5.7$ Hz, 2H), 4.72 (s, 2H); ^{13}C -NMR (75 MHz, MeOD) δ (major rotamers) 21.4 (CH_3), 22.7 (CH_2), 41.4 (CH_2), 46.1 (CH_2), 108.2 (C), 111.9 (CH), 118.5 (CH),

119.8 (CH), 122.2 (CH), 128.2 (C), 131.4 (C), 138.0 (C), 172.4 (C); δ (distinct peaks for minor rotamer) 21.9 (CH₃), 21.9 (CH₂), 45.4 (CH₂), 109.1 (C), 118.6 (CH), 119.9 (CH), 122.4 (CH), 130.8 (CH), 172.5 (C).

1-(3,4-Dihydro-1*H*-pyrido[3,4-*b*]indol-2(9*H*)-yl)propan-1-one (**3b**). The title compound was synthesized from (**2a**) (150 mg, 0.9 mmol) and propionyl chloride (0.05 mL, 0.5 mmol) to afford (**3b**) (155 mg, 78% yield) as a brown solid. m.p. 203.7–204.1 °C (lit. 204–206 °C) [52]; rotamers 1/4 (from the duplicated triplet signal (¹H) at 3.79 and 3.97 ppm); ¹H-NMR (300 MHz, CDCl₃) (major rotamer) δ 1.24 (t, *J* = 7.5 Hz, 3H), 2.51 (q, *J* = 7.5 Hz, 2H), 2.86 (t, *J* = 5.6 Hz, 2H), 3.79 (t, *J* = 5.6 Hz, 2H), 4.82 (s, 2H), 7.09 (dt, *J* = 0.9, 7.6 Hz, 1H), 7.15 (dt, *J* = 1.5, 7.6 Hz, 1H), 7.33 (d, *J* = 7.7 Hz, 1H), 7.46 (d, *J* = 7.5 Hz, 1H), 8.35 (br s, 0.6H); δ (distinct peaks for minor rotamer) 2.43 (q, *J* = 7.5 Hz, 2H), 2.81 (t, *J* = 5.6 Hz, 2H), 3.97 (t, *J* = 5.6 Hz, 2H), 4.66 (s, 2H), 7.95 (br s, 0.4H); ¹³C-NMR (75 MHz, CDCl₃) (major rotamer) δ 9.6 (CH₃), 22.0 (CH₂), 26.8 (CH₂), 40.5 (CH₂), 43.8 (CH₂), 107.8 (C), 111.0 (CH), 117.8 (CH), 119.5 (CH), 121.7 (CH), 126.8 (C), 130.6 (C), 136.2 (C), 173.2 (C); δ (distinct peaks for minor rotamer) 40.1 (CH₂), 43.0 (CH₂); HRESI-MS: calcd for C₁₄H₁₆N₂O [M+H]⁺: 229.1335, found: 229.1335.

1-(3,4-Dihydro-1*H*-pyrido[3,4-*b*]indol-2(9*H*)-yl)octan-1-one (**3c**). The title compound was synthesized from (**2a**) (108 mg, 0.6 mmol) and octanoyl chloride (0.21 mL, 1.2 mmol) to afford (**3c**) (125 mg, 41% yield) as a yellow solid; m.p. 149.9–150.0 °C; rotamers 1/3 (from the duplicated triplet signal (¹H) at 3.80 and 3.97 ppm); ¹H-NMR (300 MHz, CDCl₃) (major rotamer) δ 0.87 (t, *J* = 1.5 Hz, 3H), 1.20–1.50 (m, 10H), 2.48 (t, *J* = 7.5 Hz, 2H), 2.86 (t, *J* = 5.4 Hz, 2H), 3.80 (t, *J* = 5.7 Hz, 2H), 4.82 (s, 2H), 7.09 (t, *J* = 7.1 Hz, 1H), 7.16 (t, *J* = 7.1 Hz, 1H), 7.33 (d, *J* = 7.1 Hz, 1H), 7.46 (d, *J* = 7.1 Hz, 1H), 8.40 (br s, NH); δ (distinct peaks for minor rotamer) 2.41 (t, *J* = 7.5 Hz, 2H), 2.82 (t, *J* = 5.4 Hz, 2H), 3.97 (t, *J* = 5.7 Hz, 2H), 4.67 (s, 2H), 7.94 (br s, NH); ¹³C-NMR (75 MHz, CDCl₃) (major rotamer) δ 14.1 (CH₃), 22.1 (CH₂), 25.5 (CH₂), 29.2 (CH₂), 29.5 (2CH₂), 31.7 (CH₂), 33.7 (CH₂), 40.5 (CH₂), 44.0 (CH₂), 111.0 (CH), 117.8 (CH), 119.5 (CH), 121.7 (CH), 127.0 (C), 129.0 (C), 130.7 (C), 136.2 (C), 172.5 (C); δ (distinct peaks for minor rotamer) 22.6 (CH₂), 43.6 (CH₂), 118.3 (CH), 119.8 (CH), 122.1 (CH); HRESI-MS: calcd for C₁₉H₂₆N₂O [M+H]⁺: 299.2118, found: 299.2116.

(3,4-Dihydro-1*H*-pyrido[3,4-*b*]indol-2(9*H*)-yl)(phenyl)methanone (**3d**). The title compound was synthesized from (**2a**) (121 mg, 0.7 mmol) and benzoyl chloride (0.16 mL, 1.4 mmol) to afford (**3d**) (93 mg, 61% yield) as a yellow oil; rotamers 1/4 (from the duplicated singlet signal (¹H) at 4.46 and 4.89 ppm); ¹H-NMR (300 MHz, CDCl₃) (major rotamer) δ 2.88 (s, 2H), 3.66 (s, 2H), 4.89 (s, 2H), 7.00–7.13 (m, 2H), 7.18 (d, *J* = 5.8 Hz, 1H), 7.31–7.61 (s, 6H), 8.95 (br s, NH); δ (distinct peaks for minor rotamer) 4.07 (s, 2H), 4.46 (s, 2H), 8.34 (br s, NH); ¹³C-NMR (75 MHz, CDCl₃) (major rotamer) δ 22.1 (CH₂), 41.1 (CH₂), 46.1 (CH₂), 107.8 (C), 111.1 (CH), 117.8 (CH), 119.6 (CH), 121.8 (CH), 126.8 (C), 126.9 (2CH), 128.6 (2CH), 130.0 (C), 130.0 (CH), 136.0 (C), 136.3 (C), 171.6 (C); HR-ESI-MS [53] C₁₈H₁₆N₂O [M]: 276.1263.

(3,4-Dihydro-1*H*-pyrido[3,4-*b*]indol-2(9*H*)-yl)(furan-2-yl)methanone (**3e**). The title compound was synthesized from (**2a**) (93 mg, 0.5 mmol) and 2-furoyl chloride (0.11 mL, 1.1 mmol) to afford (**3e**) (18.7 mg, 13% yield) as a brown oil; ¹H-NMR (300 MHz, CDCl₃) δ 2.95 (s, 2H), 4.09 (br s, 2H), 4.92 (s, 2H), 6.51 (dd, *J* = 1.7, 3.4 Hz, 1H), 7.07 (d, *J* = 3.5 Hz, 1H), 7.09 (dt, *J* = 1.3, 7.2 Hz, 1H), 7.15 (dt, *J* = 1.3, 7.4 Hz, 1H), 7.31 (d, *J* = 7.2 Hz, 1H), 7.48 (d, *J* = 7.2 Hz, 1H), 7.54 (s, 1H), 8.40 (br, NH); ¹³C-NMR (75 MHz, CDCl₃) δ 20.4 (CH₂), 40.2 (CH₂), 43.5 (CH₂), 109.2 (CH), 109.6 (CH), 112.7 (C), 114.7 (CH), 116.0 (CH), 117.9 (CH), 120.1 (CH), 125.7 (C), 128.1 (C), 135.8 (C), 142.3 (CH), 146.1 (C), 158.4 (C); HRESI-MS: calcd for C₁₆H₁₄N₂O₂ [M+H]⁺: 267.1128, found: 267.1128.

2-Pentyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (**3f**). The title compound was synthesized from (**2a**) (115 mg, 0.7 mmol) and 1-bromopentane (0.25 mL, 2.0 mmol) to afford (**3f**) (93 mg, 57% yield) as a yellow solid. m.p. 110.9–112.6 °C (lit. 119–120 °C) [54]; ¹H-NMR (300 MHz, CDCl₃) δ 0.92 (t, *J* = 6.8 Hz, 3H), 1.30–1.50 (m, 4H), 1.55–1.67 (m, 2H), 2.56–2.63 (m, 2H), 2.75–2.92 (m, 4H), 3.69 (s, 2H), 7.07 (dt, *J* = 1.4, 7.0 Hz, 1H), 7.12 (dt, *J* = 1.4, 7.0 Hz, 1H), 7.26–7.33 (m, 1H), 7.46 (d, *J* = 7.2 Hz, 1H), 7.69 (br s, NH); ¹³C-NMR (75 MHz, CDCl₃)

δ 12.1 (CH₃), 19.4 (CH₂), 20.7 (CH₂), 25.3 (CH₂), 27.8 (CH₂), 48.6 (CH₂), 49.2 (CH₂), 56.0 (CH₂), 106.7 (C), 108.6 (CH), 116.0 (CH), 117.3 (CH), 119.3 (CH), 130.0 (C), 134.1 (C).

2-Octyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (**3g**). The title compound was synthesized from (**2a**) (171 mg, 1.0 mmol) and 1-bromooctane (0.34 mL, 3.0 mmol) to afford (**3g**) (119 mg, 42% yield) as a yellow solid; m.p. 105.3–106.7 °C; ¹H-NMR (300 MHz, CDCl₃) δ 0.89 (t, *J* = 6.6 Hz, 3H), 1.23–1.37 (m, 10H), 1.61, (qui, *J* = 7.5 Hz, 2H), 2.50–2.60 (m, 2H), 2.79–2.90 (m, 4H), 3.67 (s, 2H), 7.06 (t, *J* = 7.1 Hz, 1H), 7.13 (t, *J* = 7.1 Hz, 1H), 7.28 (dd, *J* = 1.4, 6.5 Hz, 1H), 7.46 (dd, *J* = 1.4, 6.5 Hz, 1H), 7.79 (br s, NH); ¹³C-NMR (75 MHz, CDCl₃) 14.1 (CH₃), 21.3 (CH₂), 22.7 (CH₂), 27.5 (CH₂), 27.6 (CH₂), 29.3 (CH₂), 29.6 (CH₂), 31.9 (CH₂), 50.5 (CH₂), 51.1 (CH₂), 57.9 (CH₂), 108.6 (C), 110.6 (CH), 117.9 (CH), 119.3 (CH), 121.3 (CH), 127.3 (CH), 131.9 (C), 136.1 (C); HRESI-MS: calcd for C₁₉H₂₈N₂ [M+H]⁺: 285.2325, found: 285.2320.

(*E*)-2-(But-2-en-1-yl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (**3h**). The title compound was synthesized from (**2a**) (310 mg, 1.8 mmol) and crotyl chloride (0.26 mL, 2.7 mmol) to afford (**3h**) (98 mg, 24% yield) as an orange solid; m.p. 82.8–84.2 °C; ¹H-NMR (300 MHz, CDCl₃) δ 1.72 (d, *J* = 5.0 Hz, 3H), 2.83–2.90 (m, 4H), 3.15 (d, *J* = 5.0 Hz, 2H), 3.59 (s, 2H), 5.53–5.74 (m, 2H), 7.06 (dt, *J* = 1.4, 7.0 Hz, 1H), 7.11 (dt, *J* = 1.4, 7.0 Hz, 1H), 7.24 (d, *J* = 6.8 Hz, 1H), 7.45 (d, *J* = 6.8 Hz, 1H), 8.02 (br s, NH); ¹³C-NMR (75 MHz, CDCl₃) δ 17.8 (CH₃), 21.1 (CH₂), 49.9 (CH₂), 50.5 (CH₂), 59.8 (CH₂), 108.3 (C), 110.7 (CH), 117.9 (CH), 119.3 (CH), 121.3 (CH), 126.8 (C), 127.2 (C), 127.5 (CH), 127.7 (CH), 129.6 (CH), 131.7 (C), 136.1 (C); HRESI-MS: calcd for C₁₅H₁₈N₂ [M+H]⁺: 227.1543, found: 227.1543.

2-Benzyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (**3i**). The title compound was synthesized from (**2a**) (50 mg, 0.29 mmol) and benzyl chloride (0.05 mL, 0.44 mmol) to afford (**3i**) (22 mg, 29% yield) as a yellow oil; ¹H-NMR (300 MHz, CDCl₃) δ 2.83 (t, *J* = 5.2 Hz, 2H), 2.93 (t, *J* = 5.2 Hz, 2H), 3.66 (s, 2H), 3.78 (s, 2H), 7.07 (dt, *J* = 1.3, 7.1 Hz, 1H), 7.12 (dt, *J* = 1.3, 7.1 Hz, 1H), 7.27–7.44 (m, 6H), 7.47 (d, *J* = 6.0 Hz, 1H), 7.66 (br s, NH); ¹³C-NMR (75 MHz, CDCl₃) δ 21.1 (CH₂), 50.2 (CH₂), 50.9 (CH₂), 61.9 (CH₂), 108.4 (C), 110.7 (CH), 117.9 (CH), 119.4 (CH), 121.4 (CH), 127.3 (CH), 128.4 (2CH), 129.2 (2CH), 131.7 (C), 136.0 (C), 138.2 (C).

3.1.4. General Procedure for the Preparation of

2-substituted-1-phenyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (**3j–3k**)

1-Phenyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (**2b**) (1 eq) was dissolved in CH₂Cl₂ (1 mL/mmol), and NEt₃ (3 eq) was added to the solution. Then, an acid halide or acyl halide was slowly added while stirring at room temperature for 24 h. Next, the product was extracted with CH₂Cl₂, and the organic layer was dried over anh. Na₂SO₄ and evaporated under reduced pressure. The crude product was purified using column chromatography (silica gel, 5% MeOH:CH₂Cl₂).

1-(1-Phenyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indol-2(9*H*)-yl)ethanone (**3j**). The title compound was synthesized from (**2b**) (117 mg, 0.47 mmol) and acetyl bromide (0.10 mL, 1.4 mmol) to afford (**3j**) (73 mg, 53% yield) as a brown solid; m.p. 236.6–237.8 °C (lit. 266 °C) [55]; ¹H-NMR (300 MHz, CDCl₃) δ 2.19 (s, 3H), 2.80–3.05 (m, 2H), 3.40–3.60 (m, 1H), 3.89 (dd, *J* = 2.6, 12.9 Hz, 1H), 7.02 (s, 1H), 7.13 (dt, *J* = 1.1, 7.1 Hz, 1H), 7.20 (dt, *J* = 1.1, 7.1 Hz, 1H), 7.28–7.40 (m, 5H), 7.54 (d, *J* = 7.1 Hz, 2H), 7.94 (br s, NH); ¹³C-NMR (100 MHz, CDCl₃) δ 21.8 (CH₂), 22.1 (CH₃), 40.6 (CH₂), 51.6 (CH), 109.9 (C), 111.1 (CH), 118.1 (CH), 119.6 (CH), 122.2 (CH), 126.6 (CH), 128.1 (C), 128.5 (2CH), 128.8 (2CH), 131.7 (C), 136.2 (C), 139.9 (C), 169.1 (C); HRESI-MS: calcd for C₁₉H₁₈N₂O [M+H]⁺: 291.1492, found: 291.1499.

2-Octyl-1-phenyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (**3k**). The title compound was synthesized from (**2b**) (87 mg, 0.35 mmol) and 1-bromooctane (0.19 mL, 1.1 mmol) to afford (**3k**) (126 mg, 93% yield) as a brown solid; m.p. 88.9–90.5 °C; ¹H-NMR (300 MHz, CDCl₃) δ 0.86 (m, 3H), 1.10–1.34 (m, 11H), 1.53 (t, *J* = 6.8 Hz, 1H), 2.30–2.42 (m, 1H), 2.54–2.66 (m, 1H), 2.73 (dq, *J* = 4.3, 9.2 Hz, 1H), 2.89 (dt, *J* = 1.2, 3.9 Hz, 1H), 2.92–3.05 (m, 1H), 3.27–3.36 (m, 1H), 4.63 (s, 1H), 7.00–7.11 (m, 2H), 7.12–7.17 (m, 1H), 7.28–7.43 (m, 5H), 7.46–7.55 (m, 1H); ¹³C-NMR (100 MHz, CDCl₃) δ 14.2 (CH₃), 21.1 (CH₂), 26.8 (CH₂), 28.8 (CH₂), 29.1 (CH₂), 29.3 (CH₂), 29.4 (CH₂), 31.8 (CH₂), 46.3 (CH₂), 53.9 (CH₂), 62.7 (CH), 108.9 (C), 110.6 (CH), 118.5 (CH), 119.4 (CH), 121.6 (CH), 127.1 (C), 128.1 (CH), 128.6

(2CH), 129.3 (2CH), 134.6 (C), 136.3 (C), 140.9 (C); HRESI-MS: calcd for C₂₅H₃₂N₂ [M+H]⁺: 361.2638, found: 361.2640.

3.2. Antifungal Activity Assay

The in vitro antifungal activity of all tetrahydro-β-carboline derivatives was evaluated on the phytopathogenic fungi of rice (*Oryza sativa*) against four fungi: *Bipolaris oryzae*, *Curvularia lunata*, *Fusarium semitectum*, and *Fusarium fujikuroi*. The tested fungi were cultured on potato dextrose agar (PDA) and incubated at 25 ± 2 °C for 7 days [56].

3.2.1. Agar Well Diffusion Method

The well diffusion test was performed using Sabouraud dextrose agar. The solution of the synthesized compounds was dissolved in methanol and acetone for (**3b**, **3c**) to a final concentration of 20 mg/mL. The solvent of the tetrahydro-β-carboline derivatives was used as the negative control, while Amphotericin B served as the positive control. The Sabouraud dextrose agar was poured into a Petri dish (9 cm in diameter) and allowed to cool. Each agar was cut out to 4 mm in diameter, and 50 μL of the test sample was placed in each well. The fungi were incubated at 30 ± 2 °C for 7 days. After the incubation period, the diameters of the fungal colonies were measured. All compounds and controls were performed in two duplicates. The mean and standard deviation were calculated.

3.2.2. Minimum Inhibitory Concentration Test

MIC assays were determined using the broth microdilution method of the National Committee for Clinical Laboratory Standards (NCCLS 2002) [57]. Primarily, the phytopathogenic fungi were grown on PDA at 28 °C for 7 days to produce conidia. The fungal colonies were covered with 5 mL of normal saline, and the suspensions were made using a fine brush. The conidia were counted in a hemacytometer, which ranged from 2 × 10⁶ to 4 × 10⁶ spore/mL. Stock solutions of 20 mg/mL were dissolved in methanol and acetone for (**3b**, **3c**). Serial dilutions of the stock solutions were performed using Sabouraud dextrose broth glucose phenol red, with the final concentration range from 2.000 to 0.001953 mg/mL. A 100 μL aliquot of the stock solutions was transferred to each of the first wells, then 100 μL/well of each suspension was dispensed into a 96-well plate. The microdilution plates were incubated at 30 ± 2 °C for 7 days of incubation. All tests were performed in three replicates. The MICs were read and interpreted, and the endpoint determination reading was performed visually based on a comparison of the growth in the wells containing the stock solutions with that of the growth control. Amphotericin B was used as the standard control, while methanol and acetone were used as the negative control.

3.2.3. Test for Inhibitory Activity against Fungal Radial Growth

Four concentrations of tetrahydro-β-carboline (**3g**), 0, 100, 250, 500, and 1000 μg/mL, were tested for antifungal activity on the radial growth of the fungi on a PDA medium. The stock solutions were put in the center of a Petri dish and then added with 20 mL of melted PDA medium. The volume of the compound was added to a Petri dish and was adjusted according to the concentration tested. The Petri dishes were slightly shaken for a smooth distribution of the tested compound into the PDA medium. Amphotericin B (250 μg/mL) was used as the standard control. Additionally, plates without the compound were used as the negative control. A mycelia plug (5 mm diam.) of the fungi was taken from the edge of a 7-day old culture and placed in the center of the PDA. The cultures were incubated at 25 ± 2 °C for 7 days. The diameter of the fungal colony was measured and recorded on day 8 of inoculation and incubation. The inhibitory activity to the radial growth was determined according to the following formula:

$$\text{IR}(\%) = \frac{\text{DC} - \text{DT}}{\text{DC}} \times 100 \quad (1)$$

IR = inhibitory activity against radial growth in percent.
DC = diameter of fungal colony without compounds (control).
DT = diameter of fungal colony treated with compound.

4. Conclusions

In summary, a series of tetrahydro- β -carbolines (**2a–2h**) was synthesized from tryptamine (**1a**) or tryptophan methyl ester (**1b**) and various aldehydes for 1–2 h via Pictet-Spengler condensation (9–80% yields), followed by *N*-alkylation or *N*-acylation with alkyl halides or acyl halides, respectively, to afford 1,2-substituted TH β Cs (**3a–3k**) (13–93% yields). The synthesized compounds were tested against the plant pathogenic fungi *Bipolaris oryzae*, *Curvularia lunata*, *Fusarium semitectum*, and *Fusarium fujikuroi*, and the results showed that the substituent at the N2 position is essential for antifungal activity. The alkyl substituent at N2 increased the inhibitory activity, especially that of the *N*-octyl derivative (**3g**), which showed the highest antifungal activity with an MIC value range of 28–200 $\mu\text{g/mL}$. Additionally, compound (**3g**) displayed good inhibitory activity to the radial growth of tested fungi at a concentration of 100 $\mu\text{g/mL}$. Accordingly, this active compound (**3g**) showed broad range of antifungal activities against four plant pathogenic fungi in this study and *N*-alkyl TH β Cs could provide useful information for further development of novel TH β Cs fungicides.

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