A NEW AND FACILE SYNTHESIS OF RUTAECARPINE ALKALOIDS

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Abstract – Relevant rutaecarpine analogues (**1a-d**) have been synthesized efficiently from the ring opened β-carboline derivatives (**3a-d**) as key intermediates. A unique one-pot reductive-cyclization as key reaction furnished the synthesis of rutaecarpine alkaloids in excellent yields. The key intermediates (**3a-d**) were prepared from tryptamine following acylation, Bischler-Napieralski cyclization, benzoylation, and oxidative cleavage of the exocyclic double bond. This new synthetic approach provides a facile access to rutaecarpine analogues with potent inhibitory effect on platelet aggregation.

Large numbers of quinazolinocarboline alkaloids including rutaecarpine (**1a**) and its analogues,[1] euxylophoricine A (**1b**) and euxylophoricine C (**1c**), isolated from the dried fruits of *Evodia rutaecarpa* and callus tissue cultured from the stem of *Phellodendron amurense*, are characterized by their potent biological activities.[2-5] For instance, they are used in Chinese herbal medicine under the name Wu-Chu-Yu for remedy such as headache, dysentery, cholera, worm infections and postpartum.[6] Rutaecarpine and its analogues were also found to possess anti-stomachic, anti-emetic, anti-nociceptive, anti-inflammatory, anti-pyretic, analgesic, astringent, anti-hypertensive, uterotonic, cycloxygenase (COX-2) inhibitory and agonist TCDD-receptor activities.[7] Furthermore, rutaecarpine can also suppress platelet plug formation in mesenteric venules and increase intracellular Ca^{2+} in endothelial cells.[8] Recently, Don et al. reported that rutaecarpine derivatives selectively inhibited human CYP1A1, CYP1A2 and

CYP2B1.[9] In view of the interesting biological properties exhibited by these rutaecarpine alkaloids, there have been interests in the development of new synthetic method for quinazolinocarboline alkaloids. Robinson and coworkers reported the first total synthesis of rutaecarpine,[10] and since then versatile routes to its derivatives have been achieved.[11] For example, Eguchi et al. applied aza-Wittig reaction for various construction of quinazolinone alkaloids including a short and facile synthesis of rutaecarpine.[11i] In our previous study, we developed a new approach toward the synthesis of quinazolinocarboline analogues using one-pot reductive–cyclization as key step.[12] Herein we report our recent studies on the total syntheses of rutaecarpine alkaloids **(Figure 1)**.

1a : $R_1 = R_2 = R_3 = H$, rutaecarpine
1b : $R_1 = H$; $R_2 = R_3 = OMe$, euxylophoricine A
1c : $R_1 = H$; R_2 , $R_3 = $ -O-CH$_2$-O- , euxylophoricine C
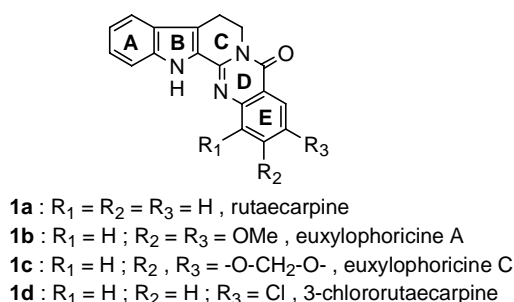1d : $R_1 = H$; $R_2 = H$; $R_3 = Cl$, 3-chlororutaecarpine

Figure 1. Rutaecarpine alkaloids

The general approach towards the synthesis of rutaecarpine **(1a)** and various analogues involved the late construction of the indole skeleton (A, B rings) by the widely-used Fischer indole synthesis through an acid-catalyzed or thermal sigmatropic rearrangement of an *N*-aryl hydrazone. On the other hand, the quinazolinocarboline backbone **(Figure 2)** has been reported to give the ring opened β-carboline derivative upon addition of base.[13] Our strategy is to synthesize a key intermediate similar to the carboline derivative, and develop a concise and new synthesis of **1a-d** complementary to efforts on synthesis of rutaecarpine alkaloids described to date.
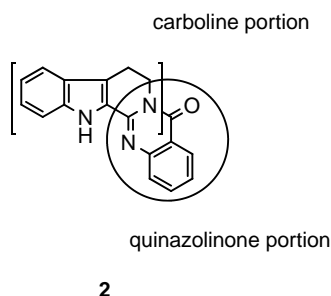

carboline portion

quinazolinone portion

2

Figure 2. Quinazolinocarboline backbone

The retrosynthetic analysis is shown in **Scheme 1**. We envisage that the reverse cyclization to rutaecarpine analogues (**1a-d**) from the nitro-intermediate of the ring opened β-carboline derivatives (**3a-d**) can be carried out in a one-pot reaction *via* reductive-cyclization. Furthermore, the 2,3,4,9-tetrahydro-β-carbolin-1-one (**3a-d**) can be readily prepared from 1-methyl-4,9-dihydro-3*H*-β-carboline (**5**) in two steps that involved the isomerization of the endocyclic double bond to the exocyclic double bond,[14] followed by an oxidative cleavage of the double bond to give the requisite carbonyl group.[15] In addition, it is also of interest to investigate the biological activities of these ring opened β-carboline derivatives synthesized. To our knowledge, no approach involving the construction of a β-carboline rings first, followed by the construction of the quinazolinone ring has been reported.
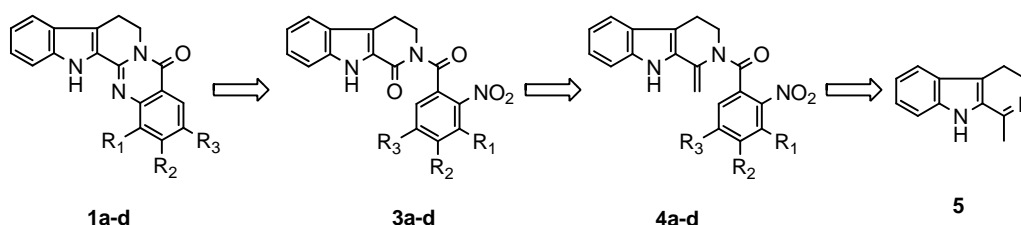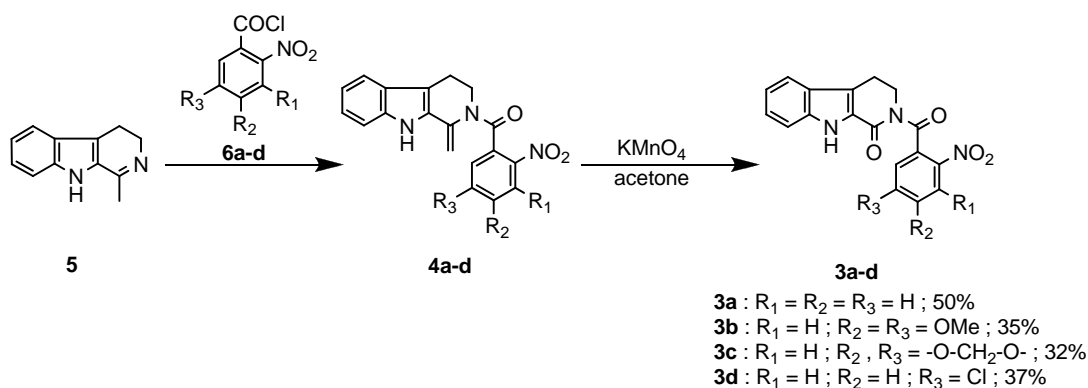

Scheme 1.   Retrosynthetic analysis of **1a-d**

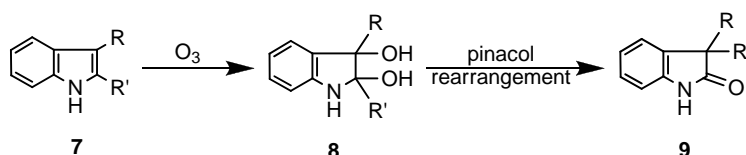1-Methyl-4,9-dihydro-3*H*-β-carboline (**5**) can be prepared from commercially available tryptamine. Treatment of tryptamine with acetic anhydride gave the *N*-acetylated adduct**,** and subsequent Bischler-Napieralski cyclization in POCl$_3$ gave β-carboline (**5**) via general procedure in good yield.[16] The reaction of β-carboline (**5**) with various benzoly chloride derivatives (**6a-d**), prepared from the corresponding known benzoic acid derivatives with SOCl$_2$, afforded the requisite intermediates **4a-d** for the synthesis of rutaecarpine alkaloids (**Scheme 2**). The unstable intermediates **4a-d** were not subjected to chromatographic purification. We then first attempted to oxidatively cleave the exocyclic double bond of crude **4a-d** under ozonolysis condition, but was unsuccessful presumably due to the reactivity of the indole 2,3-double bond toward ozone to give 2-oxoindole compound via pinacol rearrangement (**Scheme 3**).[17] Johnson-Lemieux oxidative cleavage to the double bond of **4a**, employing sodium periodate as an oxidation reagent and osmium tetroxide as a catalyst, gave the corresponding **3a** in only 15 % yield.[18] Alternatively, the use of potassium permanganate in cold acetone for the oxidative cleavage of the exocyclic double bond of **4a-d** successfully gave the desired 2,3,4,9-tetrahydro- β-carbolin-1-one derivatives (**3a-d**) in moderate yields.

The ring open β-carboline intermediates (**3a-d**) can be easily prepared in facile steps from tryptamine. A one-pot reaction was sorted for the formation of the quinazolinone ring in the reaction sequence to

synthesize rutaecarpine analogues **(Scheme 4)**. This involved the reduction of the nitro- to the amino-group, followed by an *in situ* condensation of the free amino group with the ring amide to form the quinazolinone ring.
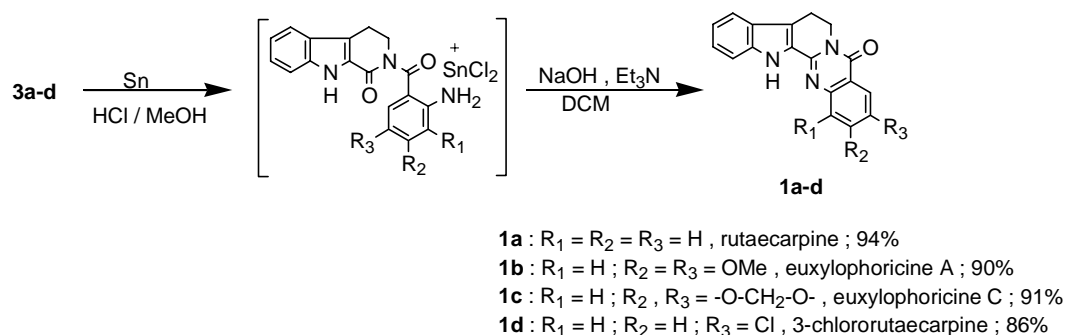

Scheme 2.   Synthesis of **3a-d**

3a : $R_1 = R_2 = R_3 = H$; 50%
3b : $R_1 = H$; $R_2 = R_3 = OMe$; 35%
3c : $R_1 = H$; R_2, $R_3 = $ -O-CH$_2$-O- ; 32%
3d : $R_1 = H$; $R_2 = H$; $R_3 = Cl$; 37%

Scheme 3.   Ozonization of indole ring

It was found that treatment of **3a-d** with tin powder in HCl/MeOH followed by basic work-up can afford rutaecarpine alkaloids **(1a-d)** in a one-pot reaction with 86 to 94 % yield. In an independent study on the search of antiplatelet aggregatory agent, we found that 3-chlororutaecarpine **(1d)** exhibited extraordinarily inhibitory effect on platelet aggregation induced by arachidonic acid **(Table 1)**.

In conclusion, a concise and facile procedure for the synthesis of rutaecarpine analogues **(1a-d)** by applying one-pot reductive-cyclization reaction as key step has been developed.   This newstrategy for the general construction of rutaecarpine alkaloids with potent inhibitory effect on platelet aggregation is noteworthy.

1a : $R_1 = R_2 = R_3 = H$, rutaecarpine ; 94%
1b : $R_1 = H$; $R_2 = R_3 = OMe$, euxylophoricine A ; 90%
1c : $R_1 = H$; R_2, $R_3 = $ -O-CH$_2$-O- , euxylophoricine C ; 91%
1d : $R_1 = H$; $R_2 = H$; $R_3 = Cl$, 3-chlororutaecarpine ; 86%

Scheme 4.   One-pot reductive-cyclization synthesis of **1a-d**

Table 1. Inhibitory effect of **1a-d** as specific antagonist agents on the aggregation of washed rabbit platelets induced by thrombin, arachidonic acid, collagen and PAF.[*]

agent	conc. (μg/mL)	Thr. (0.1 unit/mL)	A.A. (100 μM)	Col. (10 μM)	PAF (2 μg/mL)
Control		88.2 ± 0.8 % (4)	90.1 ± 0.4 % (6)	88.4 ± 1.9 % (5)	88.5 ± 1.0 % (4)
1a	100	85.7 ± 2.4 % (3)	85.2 ± 5.8 % (3)	82.1 ± 1.9 % (3)	79.6 ± 3.1 % (5)
1b	100	89.7 ± 1.6 % (3)	00.0 ± 0.0 % (4)	78.5 ± 5.4 % (3)	60.4 ± 7.3 % (3)
	50		37.6 ± 19.3 % (3)		
	20		79.2 ± 4.1 % (3)		
1c	100	89.8 ± 2.2 % (3)	00.0 ± 0.0 % (5)	80.6 ± 2.0 % (3)	65.4 ± 4.7 % (3)
	50		40.0 ± 0.4 % (3)		
	20		87.7 ± 9.7 % (3)		
1d	100	88.8 ± 2.2 % (3)	00.0 ± 0.0 % (5)	82.6 ± 2.0 % (3)	75.4 ± 4.7 % (3)
	5		00.0 ± 0.0 % (3)		
	2		17.7 ± 9.7 % (3)		
	1		74.6 ± 4.7 % (3)		

*Platelets were pre-incubated with 0.5% DMSO (control) or **1a-1d** for 3 min, then the inducer was added to trigger aggregation.
%: aggregation (mean ± S. E (n))

EXPERIMENTAL

All melting points were taken with a Thomas-Hoover capillary melting point apparatus and are uncorrected. [1]H nuclear magnetic resonance spectra were recorded on Varian Associates VXR-300 (300 MHz) spectrometer and are reported in parts per million from internal tetramethylsilane on the scale. Assignments are based on multiplicity, coupling constant and chemical shift data and in certain instances may be regarded as tentative. [13]C nuclear magnetic resonance spectra were rcorded on a VXR-300. ^{13}C-NMR spectra were recorded as Broad-Band, Off-Resonance-Decoupled or DEPT (Distortionless Enhancement by Polarization Transfer) spectra.   Infrared spectra were taken with a Bio-Rad FTS-40 instrument. Low resolution mass spectra were recorded on Hitachi M-52 instrument at an ionization energy of 70 ev.   Samples on which exact masses were measured exhibited no significant peaks at *m/e* values greater than those of the parent.   Solvents and reagents were dried and purified prior to use when deemed necessary. High resolution mass spectra were recorded on Jeol JMS-HX110 instrument.   All reaction temperatures refer to that of the reaction mixture unless indicated otherwise. Column chromatography was performed over EM laboratories silica 60 (70-230 mesh). Ethyl acetate and *n*-hexane, used as eluents in column chromatography, were distilled prior to use. The order of experimental procedures generally follows their order of appearance in the text.

General procedure for preparation of 3a-d

To a stirred solution of 2-nitrobenzoic acid (1.085 g, 6.50 mmol) in CH_2Cl_2 (47 mL) stirred at rt was slowly added $SOCl_2$ (5.57 mL). The reaction mixture was refluxed for 1h and concentrated in vacuo to obtain the acid chloride (**6a**) as a crude residue. The residue was dissolved in 40 mL of CH_2Cl_2 and slowly added to a solution of compound **5** (1000 mg, 5.95 mmol) in 57 mL of CH_2Cl_2. The reaction mixture was stirred at rt for 2 h and concentrated in vacuo to afford the crude residue. The residue was worked-up in brine and extracted with $CHCl_3$. The organic layer was dried and concentrated in vacuo to give the crude product **4a** ready for the following oxidative cleavage without further purification. The crude product **4a** was dissolved in cold acetone, slowly added $KMnO_4$ and the reaction mixture was monitored by TLC. After the requisite reaction was done, the reaction mixture was concentrated in vacuo, the residue was worked-up with aqueous ammonium chloride solution and extracted with $CHCl_3$. The organic layer was washed with brine, dried and concentrated in vacuo to give the crude product, which was subjected to column chromatography to obtain the pure product **3a** (996 mg, 2.97 mmol) with a total yield of 50 %.

N-(2-Nitrobenzoyl)-1-oxo-1,2,3,4-tetrahydro-β-carboline (3a): mp 109-111 °C (MeOH/CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) 3.21 (t, J = 6.0 Hz, 2H), 4.56 (br, 2H), 7.16-7.21 (m, 1H), 7.25-7.27 (m, 1H), 7.33-7.39 (m, 2H), 7.49-7.55 (m, 1H), 7.71-7.83 (m, 2H), 8.19 (dd, J = 1.2, 8.4 Hz, 1H), 8.76 (brs, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) 20.51, 44.01, 112.58, 120.93, 120.98, 123.99, 124.67 (2C), 125.16, 126.83, 126.88, 129.12, 134.09, 135.29, 138.62, 144.60, 160.03, 168.22; IR ($CHCl_3$, cm^{-1}) 3457 (NH), 1684 (C=O), 1680 (C=O), 1530 (NO_2), 1347 (NO_2); MS m/z (%) 335 (M^+, 35.6%), 289 (M^+-46, 91.6%), 185 (M^+-150, 51.9%), 184 (M^+-151, 45.8%), 56 (M^+-179, 67.3%), 150 (M^+-85, 50.4%), 129 (M^+-206, 100%), 128 (M^+-207, 85.5%); HRMS m/z: Calcd for $C_{18}H_{13}N_3O_4$: 335.0890. Found: 335.0893. Anal. Calcd for $C_{18}H_{13}N_3O_4$: C, 64.47; H, 3.91; N, 12.53; Found: C, 64.52; H, 3.93; N, 12.45.

N-(4,5-Dimethoxy-2-nitrobenzoyl)-1-oxo-1,2,3,4-tetrahydro- β-carboline (3b): mp 117-119 °C (MeOH/CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) 3.22 (t, J = 6.3 Hz, 2H), 3.94 (s, 3H), 3.95 (s, 3H), 4.57 (t, J = 6.3Hz, 2H), 6.87 (s, 1H), 7.18 (t, J = 6.9Hz, 1H), 7.27 (d, J = 8.4Hz, 1H), 7.36 (t, J = 6.9Hz, 1H), 7.64 (d. J = 8.1Hz, 1H), 7.68 (s, 1H), 8.81 (brs, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) 20.53, 44.11, 56.36, 56.54, 106.73, 108.55, 112.49, 121.00, 121.04, 124.70, 124.76, 125.32, 126.95, 129.65, 137.60, 138.58, 148.74, 154.02, 160.05, 168.10; IR ($CHCl_3$, cm^{-1}) 3456 (NH), 1704 (C=O), 1684 (C=O), 1518 (NO_2), 1333 (NO_2); MS m/z (%) 395 (M^+, 0.1%), 350 (M^+-45, 2.37%), 349 (M^+-46, 100%), 136 (M^+-259, 39.1%), 129 (M^+-266, 32.6%), 128 (M^+-267, 26.7%), 93 (M^+-302, 25.3%); HRMS m/z: Calcd for $C_{20}H_{17}N_3O_6$: 395.1126. Found: 395.1124. Anal. Calcd for $C_{20}H_{17}N_3O_6$: C, 60.76; H, 4.33; N, 10.63.

Found: C, 60.81; H, 4.37; N, 10.58.

N-(4,5-Dimethylenedioxy-2-nitrobenzoyl)-1-oxo-1,2,3,4-tetrahydro- β-carboline (3c): mp 111-113 °C (MeOH/CH$_2$Cl$_2$); ^{1}H NMR (300 MHz, CDCl$_3$)   3.22 (t, J = 6.3 Hz, 2H), 4.57 (t, J = 6.3 Hz, 2H), 6.14 (s, 2H), 6.75 (s, 1H), 7.19-7.21 (m, 1H), 7.30-7.40 (m, 2H), 7.64 (s, 1H), 7.65 (d, J = 3.6 Hz, 1H), 8.68 (brs, 1H, NH); ^{13}C NMR (75 MHz, CDCl$_3$)   20.57, 44.10, 103.46, 104.81, 106.16, 112.46, 121.12, 121.17, 124.73, 124.86, 125.31, 127.09, 131.98, 138.52, 139.26, 148.11, 152.71, 159.98, 167.62; IR (CHCl$_3$, cm^{-1}) 3464 (NH), 1674 (C=O), 1669 (C=O), 1552 (NO$_2$), 1340 (NO$_2$); MS m/z (%) 379 (M$^+$, 80.4%), 129 (M$^+$-250, 63.59%), 120 (M$^+$-259, 71%), 55 (M$^+$-324, 98.9%), 44 (M$^+$-335, 100%); HRMS m/z: Calcd for C$_{19}$H$_{13}$N$_3$O$_6$: 379.0784. Found: 379.0788. Anal. Calcd for C$_{19}$H$_{13}$N$_3$O$_6$: C, 60.16; H, 3.45; N, 11.08. Found: C, 60.20; H, 3.50; N, 11.02.

N-(5-Chloro-2-nitrobenzoyl)-1-oxo-1,2,3,4-tetrahydro- β-carboline   (3d):   mp   108-110   °C (MeOH/CH$_2$Cl$_2$); ^{1}H NMR (300 MHz, CDCl$_3$)   3.24 (t, J = 6.0 Hz, 2H), 4.57 (t, J = 6.0 Hz, 2H), 7.20-7.23 (m, 1H), 7.32-7.39 (m, 3H), 7.65-7.68 (m, 2H), 8.21 (s, 1H), 8.62 (brs, 1H, NH); ^{13}C NMR (75 MHz, CDCl$_3$)   20.58, 44.07, 112.48, 121.17, 124.32, 124.79, 124.92, 125.04, 127.25, 128.03, 133.66, 134.16, 135.20, 138.58(2C), 145.25, 159.93, 167.26; IR (CHCl$_3$, cm^{-1}) 3461 (NH), 1695 (C=O), 1686 (C=O), 1530 (NO$_2$), 1347 (NO$_2$); MS m/z (%) 369 (M$^+$, 18%), 307 (M$^+$-62, 24.6%), 154 (M$^+$-215, 100%), 136 (M$^+$-233, 96.0%), 89 (M$^+$-280, 65.6%), 77 (M$^+$-292, 66.7%); HRMS m/z: Calcd for C$_{18}$H$_{12}$ClN$_3$O$_4$: 369.0502. Found: 369.0515. Anal. Calcd for C$_{18}$H$_{12}$ClN$_3$O$_4$: C, 58.47; H, 3.27; N, 11.36. Found: C, 58.55; H, 3.30; N, 11.29.

General procedure for preparation of 1a-d

To a stirred solution of   **3a** (87 mg, 0.26 mmol) in 16 mL of MeOH cooled with ice-bath was slowly added tin powder (90.6 mg, 0.78 mmol).   The reaction mixture was slowly added 2 mL of concentrated HCl in ice-bath.   The solution was   then stirred at rt for extra 12 h followed by basic work-up with NaOH solution, and then was added small amount of CHCl$_3$ and triethyl amine to stir another 3 h.   The reaction mixture was added brine and extracted with CHCl$_3$.   The organic layer was washed with brine, dried and concentrated in vacuo to afford the crude product **1a**,   which was subjected to chromatograhpy to obtain the pure **1a** (69.9 mg, 0.24 mmol) with a total yield of 94 %.

Rutaecarpine (1a): mp 254-255 °C (lit.,^{11q} mp 257-259 °C); ^{1}H NMR (300 MHz, CDCl$_3$)   3.24 (t, J = 6.9 Hz, 2H), 4.59 (t, J = 6.9 Hz, 2H), 7.19 (t, J = 8.4 Hz, 1H), 7.34 (dt, J = 1.2, 6.8 Hz, 1H), 7.41-7.67 (m, 2H), 7.63-7.73 (m, 3H), 8.32 (dd, J = 1.2, 7.8 Hz, 1H), 9.27 (brs, 1H,NH); ^{13}C NMR (75 MHz, CDCl$_3$)

19.68, 41.12, 112.07, 118.33, 120.08, 120.62, 121.37, 125.58, 125.64, 126.19, 126.61, 127.23, 134.32(2C), 138.27, 144.95, 147.52, 161.59; IR (CHCl$_3$, cm^{-1}) 3463 (NH), 1676 (C=O); MS m/z (%) 287 (M$^+$, 79.2%), 286 (M$^+$-1, 100%); HRMS m/z: Calcd for C$_{18}$H$_{13}$N$_3$O: 287.1054. Found: 287.1055.

Euxylophoricine A (1b): mp 293-295 °C (lit.,[13] mp 294-295 °C); ^{1}H NMR (300 MHz, CDCl$_3$) 3.23 (t, J = 7.0 Hz, 2H), 3.98 (s, 3H), 4.01(s, 3H), 4.59 (t, J = 7.0 Hz, 2H), 7.06 (s, 1H), 7.19 (t, J = 7.8Hz, 1H), 7.33 (dd, J = 7.8, 8.1 Hz, 1H), 7.42 (d, J = 8.1 Hz, 1H), 7.63 (d, J = 8.1 Hz, 1H), 7.66 (s, 1H), 9.22 (brs, 1H, NH); ^{13}C NMR (75 MHz, CDCl$_3$) 19.69, 41.10, 56.22, 56.35, 106.41, 107.12, 111.97, 114.50, 117.64, 119.99, 120.62, 125.36, 125.73, 127.35, 138.13, 143.68, 143.99, 148.76, 154.98, 160.90; IR (CHCl$_3$, cm^{-1}) 3461 (NH), 1663 (C=O); MS m/z (%) 347 (M$^+$, 100%), 332 (M$^+$-25, 22.7%), 128 (M$^+$-219, 13.4%), 55 (M$^+$-292, 48.6%), 43 (M$^+$-304, 74.6%); HRMS m/z: Calcd for C$_{20}$H$_{17}$N$_3$O$_3$: 347.1264. Found: 347.1265.

Euxylophoricine C (1c): mp 307-308 °C (lit.,[13] mp 310-312 °C); ^{1}H NMR (300 MHz, CDCl$_3$) 3.27 (t, J = 6.9 Hz, 2H), 4.57 (t, J = 6.9 Hz, 2H), 6.10 (s, 2H), 7.03 (s, 1H), 7.18 (t, J = 6.9 Hz, 1H), 7.36 (t, J = 6.9 Hz, 1H), 7.44 (d, J = 6.9 Hz, 1H), 7.63 (d, J = 6.9 Hz, 1H), 7.64 (s, 1H), 9.07 (brs, 1H, NH); ^{13}C NMR (75 MHz, CDCl$_3$) 19.88, 41.89, 102.53, 104.29, 105.96, 111.97, 116.10, 117.64, 120.00, 120.60, 125.38, 125.70, 127.24, 138.11, 143.81, 143.58, 147.10, 153.42, 160.87; IR (CHCl$_3$, cm^{-1}) 3469 (NH), 1663 (C=O); MS m/z (%) 331 (M$^+$, 100%), 330 (M$^+$-1, 94%); HRMS m/z: Calcd for C$_{19}$H$_{13}$N$_3$O$_3$: 331.0957. Found: 331.0957.

3-Chlororutaecarpine (1d): mp 290-291 °C (lit.,[13] mp 290-293 °C); ^{1}H NMR (300 MHz, DMSO-d_6) 3.17 (t, J = 6.9 Hz, 2H), 4.43 (t, J = 6.9 Hz, 2H), 7.09 (t, J = 7.2-7.5 Hz, 1H), 7.28 (t, J = 7.5-7.8 Hz, 1H), 7.46-7.50 (m, 2H), 7.62-7.66 (m, 2H), 8.13 (d, J = 8.4 Hz, 1H), 11.86 (brs, 1H,NH); ^{13}C NMR (75 MHz, DMSO-d_6) 19.05, 41.09, 112.82, 118.79, 119.68, 120.02, 120.27, 124.99, 125.22, 125.51, 126.25, 126.93, 128.86, 139.01, 139.09, 146.73, 148.73, 160.26; IR (CHCl$_3$, cm^{-1}) 3451 (NH), 1675 (C=O); MS m/z (%) 323 (M$^+$+2, 27.0%), 322 (M$^+$+1, 42.4%), 321 (M$^+$, 80.8%), 320 (M$^+$-1, 100%), 128 (M$^+$-195, 19.2%); HRMS m/z: Calcd for C$_{18}$H$_{12}$ClN$_3$O: 321.0632. Found: 321.0643.

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