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ARTICLE

Application of metal free aromatization to total synthesis of perlolyrin, flazin, eudistomin U and harmane

Srinath Santhanam[1] | **Abinaya Ramu**[1] | **Baskar Baburaj**[1] | **Balasubramanian Kalpatu Kuppusamy**[2]

[1]Laboratory of Sustainable Chemistry, Department of Chemistry, SRM Institute of Science and Technology, Kancheepuram, India

[2]Department of Biotechnology, Indian Institute of Technology Madras, Chennai, India

Correspondence
Baskar Baburaj, Laboratory of Sustainable Chemistry, Department of Chemistry, SRM Institute of Science and Technology, Kattankulatur 603 203, Kancheepuram Dt., Tamilnadu, India.
Email: bbaskar10@gmail.com

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Abstract

Application of our recently reported metal free reaction conditions to the total synthesis of the four different and selective biologically interesting β-carboline natural products is reported. Using this simple methodology, flazin, perlolyrine, eudistomin U and harmane containing heteroaryl and alkyl substituents at C1 position were synthesized in good yields.

1 | INTRODUCTION

The β-carboline unit is one of the versatile indole-based heterocycles, and this basic ring skeleton is found in a variety of alkaloids,[1] pharmaceuticals,[2] agrochemicals[3] and functional materials.[4] Particularly, there are nearly 64 identified β-carboline alkaloids distributed across the eight plant families. Importantly, aromatic β-carboline natural products (Figure 1) eudistomin U, isoeudistomin, flazin, flazinamide, perlolyrine, harmane and harmine exhibit a wide range of biological activities such as antimalarial,[5] antiviral,[6] neuroprotection,[7] anti-HIV,[8] anticancer,[9] etc. Therefore, there has been considerable interest in the synthesis of β-carbolines.[10] Aromatiszation of the tetradhydro-β-carboline ring constitutes a key step in all these synthetic approaches.[11]

Typical approach involves decarboxylative/dehydrogenative aromatization of tetrahydro-β-carbolines. The decarboxylative aromatization of tetrahydro-β-carbolines is accomplished by using reagents such as $K_2Cr_2O_7$,[12] SeO_2,[13] $KMnO_4$,[14] MnO_2,[15] Pd/C,[16] $Pb(OAc)_4$.[17]

However, most of these methods require harsh conditions. Other reagents such as chloranil,[18] DDQ,[19] trichloroisocyanuric acid,[20] $PhI(OAc)_2$,[21] N-chlorosuccinimide[22] (NCS) and IBX[23] have also been employed for the aromatization but these methods have their own drawbacks such as stoichiometric by product generation, use of expensive reagents, low yields or lack of general application. We had recently reported a metal free one pot synthesis of various β-carbolines involving a domino Pictet-Spengler reaction and aromatization using oxygen in N-methyl-2-pyrolidone (NMP) at 140°C was efficiently established.[24] Now we demonstrate the

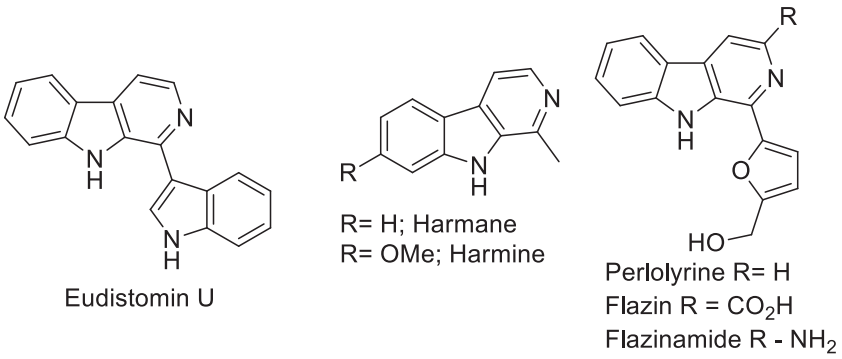
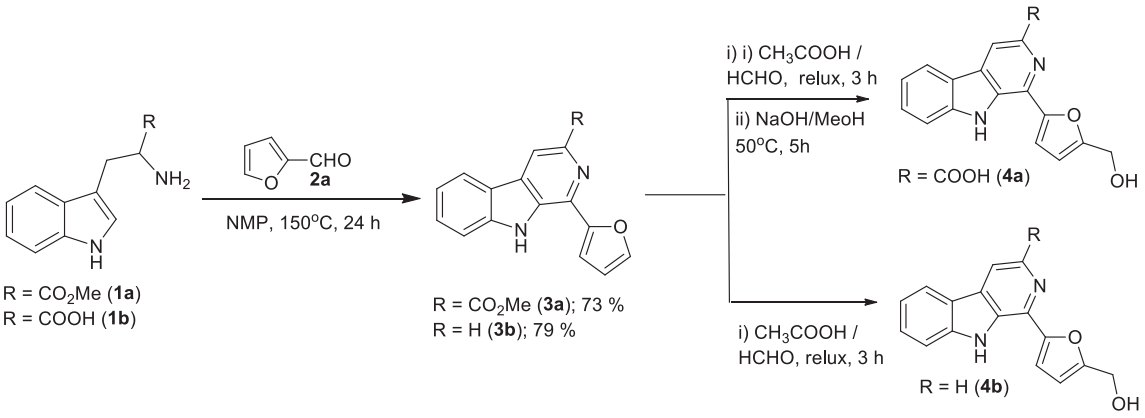


FIGURE 1 Examples of naturally occurring biologically active β-carbolines



SCHEME 1 Syntheses of β-carboline alkaloid natural products: flazin and perlolyrine

application of this methodology for the synthesis of a few biologically active β-carboline natural products. Hence, we envisioned to employ our methodology for the synthesis of few β-carboline natural products viz., flazin, perlolyrine, eudistomin U and harmane.

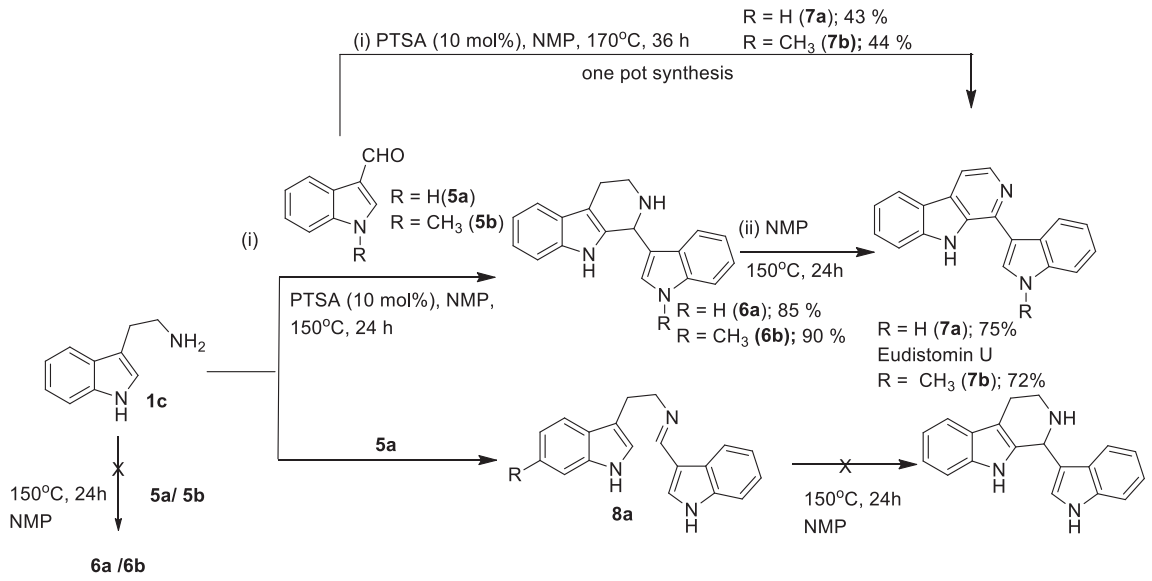
2 | RESULTS AND DISCUSSION

2.1 | Synthesis of perlolyrine and flazin

We have successfully demonstrated the substrate scope of our novel aromatization reaction of tetrahydro-β-carbolines by oxygen in NMP at 150°C by extending to the total syntheses of alkaloids flazin (**4a**) and perlolyrine (**4b**) as shown in Scheme 1. These alkaloids have been obtained from several natural sources such as plants, bacteria, Japanese sake and soy sauce.[25] Flazin (**4a**), perlolyrine (**4b**) alkaloids are found to display strong fluorescence.[26] Recent report on fazin (**4a**) shows anti-HIV activity.[27] There are a few reports[28] on total syntheses of alkaloids flazin (**4a**) and perlolyrine (**4b**) but most of them involve either expensive or toxic metal catalyzed aromatization reactions. Flazin and Perlolyrine were obtained in overall yields 63% and 58%, respectively.[28a] Herein, we describe the total syntheses of alkaloids flazin (**4a**) and perlolyrine (**4b**) using our novel aromatization reaction of tetrahydro-β-carbolines by oxygen in NMP at 150°C as depicted in Scheme 1. The methodology involved the one pot Pictet-Spengler reaction of tryptophan methyl ester (**1a**) and tryptophan (**1b**) with 2-furaldehyde (**2a**) followed by aromatization in presence of oxygen at 150°C to give the β-carbolines **3a** and **3b** in 73% and 79% yields, respectively. Next, hydroxymethylation of compounds 3a with HCHO in AcOH and then hydrolysis of methyl ester afforded the flazin **4a** in 65% yields whereas hydroxymethylation of compounds **3b** with HCHO in AcOH afforded perlolyrine **4b** in 80% by following the procedure reported in literature.[28a] Thus, flazin **4a** was synthesized from tryptophan methyl ester in four steps in 47.5% overall yield and perlolyrine **4b** was synthesized from tryptamine in three steps in 62% overall yield (Figure S1).

2.2 | Synthesis of eudistomin U

Eudistomin U (Figure 1) exhibits DNA-binding and antimicrobial activities[29] and syntheses have been reported for eudistomin U.[30] All of them use metal catalysts, toxic, expensive reagents or involve multiple steps and the overall yield in most of these routes is moderate.



SCHEME 2 Syntheses of alkaloid natural products: edistomin U

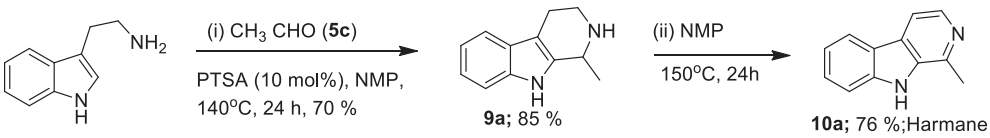
Initially, we attempted to synthesize eudistomin U directly from the indole aldehyde **5a** and tryptamine **1c** using our domino methodology (Scheme 2). When a mixture of **1c** with **5a** was heated in NMP at 150°C under oxygen atmosphere, the reaction did not yield the desired product probably due to the diminished reactivity of the aldehyde which is a vinylogous amide (**5a**). Under these conditions, N-methylindole-3-aldehyde **5b** also failed to undergo any reaction with 1c. The preformed imine, 8a prepared by heating a mixture of 1c and 5a in toluene,[31] also was unreactive when heated in NMP at 150°C under oxygen atmosphere evidently due to the absence of any acid in the system. However, when a mixture of 1c with 5a was heated in presence of p-toluenesulphonic acid (PTSA) in NMP at 150°C under nitrogen atmosphere, it gave rise to the tetrahydro-β-carboline (**6a**) in 85% yield (Scheme 2), which was characterized by the ^{1}H and ^{13}C NMR spectroscopic techniques (Figure S1). To our delight and as expected, when the same reaction was carried out at 170°C for 36 h in oxygen atmosphere, it furnished eudistomin U **7a** in 43% yield (Scheme 2). Furthermore, when **6a** was heated at 150°C for 24 h in NMP, it underwent the aromatization and afforded eudistomin U **7a** in 75% yield. A similar reaction with 5b furnished the N-methyl eudistomin U **7b** in 44% yield when heated in NMP at 170°C for 36 h as outlined in Scheme 2. Reported literature[23] method for the synthesis of **7a** by Panarese et al involves the condensation of tryptophan methyl ester with N-acetyl-indole-3-aldehyde in benzene under reflux to form the imine, cyclisation of the imine to the 3-methoxycarbonyl tetrahydro-β-carboline intermediate using trifluoroacetic acid and chloroform mixture in 2:1 ratio and aromatization of the 3-methoxycarbonyl tetrahydro-β-carboline derivative by IBX followed by hydrolysis of the methyl ester and decarboxylation. This sequence involves not only many steps but also harsh reagents or conditions and the overall yield is rather low. Particularly, the yield in the final decarboxylation is also low. Further aromatization by IBX worked out only in the case of 3-methoxycarbolyl tetrahydro-β-carboline but not in the case of simple tetrahydro-β-carbolines.

2.3 | Synthesis of harmane

Another β-carboline alkaloid, harmane was found to display antitumor activities via different mechanisms such as inserting into DNA or inhibiting Topoisomerase I and II, cyclin-dependent kinases (CDK), PLK or MAO.[32] Though many syntheses have been reported for harmane, most of these methods involve decarboxylation followed by aromatization.[33] In the present work, we have successfully synthesized harmane (**10a**) by the Pictet Spengler reaction[34] of the reaction of tryptamine (**1c**) with acetaldehyde (**5c**) to provide the corresponding tetrahydro-β-carboline (**9a**) in 85% yield which was subjected to the aromatization in presence of oxygen at 150°C in NMP to obtain harmane **10a** in 76% (Scheme 3; Figure S1).

3 | CONCLUSION

We have demonstrated the application of our one pot Pictet-Spenger reaction and novel methodology for



SCHEME 3 Synthesis of alkaloid natural product: harmane

aromatization reaction of tetrahydro-β-carbolines by oxygen in NMP at 150°C to the total synthesis of β-carboline derived indole alkaloids, flazin, perlolyrine, eudistomin U and harmane. These alkaloids were obtained in good yields in a straight forward way under metal free reaction conditions.

4 | EXPERIMENTAL

General: All reactions were carried out either under an argon or oxygen atmosphere unless otherwise noted. All chemicals used in the reactions such as tryptophan, tryptamine, aliphatic aldehyde and hetero aldehyde were purchased from Aldrich and used without further purification. $CDCl_3$ and DMSO-d_6 for NMR sample preparation were purchased from Aldrich. Dry solvent, NMP, used in synthesis with minimum purity of 99.9% was purchased from Aldrich. Thin-layer chromatography (TLC) was performed using 60 mesh silica gel plates visualized with short-wavelength UV light (254 nm). Silica gel 60 (230-400 mesh) was used for flash column chromatography. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 500 instrument (500 MHz for ^{1}H and 125 MHz for ^{13}C NMR). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants *J* are reported in hertz.

4.1 | Synthesis of natural product flazin (4a)

Step 1: Synthesis of methyl 1-(furan-2-yl)-9H-pyrido [3,4-b]indole-3-carboxylate (**3a**): In a 5 mL RB flask were added a mixture of 2-furaldehyde (**2a**) (23 μL, 0.22 mmol, 1.2 equiv.,), tryptophan methyl ester (**1a**) (44 mg, 0.20 mmol, 1 equiv.) in NMP (1 mL) and the resulting mixture was heated at 150°C under oxygen atmosphere for 24 h. After the reaction was complete, the reaction mixture was concentrated under reduced pressure using rotary evaporator. The crude product thus obtained was purified by flash column chromatography on silica gel using mixture of hexane-ethyl acetate (70:30) as eluent to obtain the product **3a** in 73% yield (43 mg, 0.144 mmol). 1-(5-(Hydroxymethyl)furan-2-yl)-9H-pyrido[3,4-b]indole-3-carboxylic acid (flazin **4a**) was achieved from **3a** by following the procedure reported in the literature.[28a]

Flazin **4a**: ^{1}H NMR (500 MHz, DMSO-d6) δ 8.78 (s, 1H), 8.34 (d, *J* = 7.8 Hz, 1H), 7.83 (d, *J* = 8.2 Hz, 1H), 7.62 (t, *J* = 7.6 Hz, 1H), 7.43 (d, *J* = 2.9 Hz, 1H), 7.33 (t, *J* = 7.5 Hz, 1H), 6.61 (d, *J* = 3.1 Hz, 1H), 4.65 (s, 2H). ^{13}C NMR (125 MHz, DMSO-d6) δ 167.63, 157.14, 151.79, 141.75, 132.71, 132.00, 130.27, 129.43, 129.36, 122.29, 121.20, 121.13, 116.01, 113.30, 111.50, 110.05, 56.11. HRMS (ESI) m/z calcd for $C_{17}H_{12}N_2O_4Na$ $[M + Na]^+$: 331.0695, found: 331.0697.

4.2 | Synthesis of natural product perlolyrine (4b)

In a 5 mL RB flask were added a mixture of 2-furaldehyde (**2a**) (23 μL, 0.22 mmol, 1.2 equiv.,), tryptophan (**1b**) (45 mg, 0.20 mmol, 1 equiv.) in NMP (1 mL) and the resulting mixture was heated at 150°C under oxygen atmosphere for 24 h. After the reaction was complete, the reaction mixture was concentrated under reduced pressure using rotary evaporator. The crude product thus obtained was purified by flash column chromatography on silica gel using mixture of hexane-ethyl acetate (70:30) as eluent to obtain the product **3b** in 79% yield (37 mg, 0.158 mmol). (5-(9H-pyrido[3,4-b]indol-1-yl)furan-2-yl)methanol (perlolyrine **4b**) was achieved from compound **3b** by following the procedure reported in the literature.[28a]

Perlolyrine **4b**: ^{1}H NMR (500 MHz, DMSO-d6) δ 8.33 (d, *J* = 5.1 Hz, 1H), 8.22 (d, *J* = 7.9 Hz, 1H), 8.05 (d, *J* = 5.2 Hz, 1H), 7.75 (d, *J* = 8.2 Hz, 1H), 7.61-7.50 (m, 1H), 7.34-7.24 (m, 1H), 7.20 (d, *J* = 3.3 Hz, 1H), 6.59 (d, *J* = 3.3 Hz, 1H), 4.65 (s, 2H).^{13}C NMR (125 MHz, DMSO-d6) δ 156.72, 152.63, 141.33, 138.47, 133.28, 130.70, 130.05, 129.05, 122.08, 120.85, 120.33, 114.23, 112.85, 110.15, 109.94, 56.16. HRMS (ESI) calcd for $C_{16}H_{13}N_2O_2$ $[M + H]^+$: 265.0977, found: 265.0974.

Synthesis of natural product, eudistomin U and its N-methylated derivative (**7a** and **7b**):

Step 1: In a 5 mL RB flask were added a mixture of 1*H*-indole-3-carbaldehyde (**9a**) (32 mg, 0.22 mmol, 1.2 equiv.,), tryptamine (**1a**, 32 mg, 0.20 mmol, 1 equiv.,) and *p*-toluene sulphonic acid (3.44 mg, 0.02 mmol, 0.1 equiv.,) in NMP (1 mL) and the resulting mixture was heated at 150°C under argon atmosphere for 24 h. After the reaction

was complete, the reaction mixture was concentrated under reduced pressure using rotary evaporator. The crude product thus obtained was purified by flash column chromatography on silica gel using mixture of DCM-Methanol (95:5) as eluent to obtain the product **6a** in 85% yield (48.8 mg, 0.17 mmol).

Compound **6a**.[21] Yield: 85% yield (48 mg); ^{1}H NMR (500 MHz, DMSO-d6) δ 7.46 (d, J = 7.7 Hz, 1H), 7.40 (d, J = 8.1 Hz, 1H), 7.31 (d, J = 8.0 Hz, 1H), 7.22 (d, J = 7.5 Hz, 1H), 7.17 (s, 1H), 7.07 (t, J = 7.6 Hz, 1H), 7.04-6.95 (m, 2H), 6.88 (t, J = 7.5 Hz, 1H), 5.45 (s, 1H), 3.20 (dt, J = 11.8, 4.8 Hz, 1H), 2.98 (ddd, J = 12.3, 7.4, 4.9 Hz, 1H), 2.89-2.79 (m, 1H), 2.78-2.69 (m, 1H); ^{13}C NMR (125 MHz, DMSO-d6) δ 136.8, 136.1, 136.0, 127.3, 126.6, 124.9, 121.6, 120.9, 119.7, 119.0, 118.7, 118.0, 115.7, 111.9, 111.5, 108.0, 49.8, 42.1, 22.37.

Step 2: In a 5 mL RB flask was added compound **6a** (57.4 mg, 0.20 mmol) in NMP (1 mL) and the resulting mixture was heated at 150°C under oxygen atmosphere for 24 h. After the reaction was complete, the reaction mixture was concentrated under reduced pressure using rotary evaporator. The crude product thus obtained was purified by flash column chromatography on silica gel using mixture of DCM-Methanol (95:5) as eluent to obtain the product **7a** in 89% yield (50.4 mg, 0.178 mmol).

Eudistomin U[22] (**7a**). Yield: 89% yield (50 mg); ^{1}H NMR (500 MHz, DMSO-d6) δ 11.72 (s, 1H), 11.32 (s, 1H), 8.54 (d, J = 8.0 Hz, 1H), 8.45 (d, J = 5.2 Hz, 1H), 8.29 (d, J = 2.6 Hz, 1H), 8.24 (d, J = 7.8 Hz, 1H), 7.97 (d, J = 5.2 Hz, 1H), 7.70 (d, J = 8.2 Hz, 1H), 7.54 (dd, J = 14.3, 7.6 Hz, 2H), 7.26 (t, J = 7.5 Hz, 1H), 7.22 (t, J = 7.4 Hz, 1H), 7.15 (t, J = 7.4 Hz, 1H).^{13}C NMR (125 MHz, DMSO-d6) δ 141.3, 140.8, 138.3, 137.0, 132.5, 128.7, 128.2, 126.6, 126.5, 122.7, 122.5, 121.9, 121.6, 120.3, 119.9, 112.9, 112.1. High-resolution mass spectrum (ESI) m/z 284.1182 $[M + H]^+$; calcd for $C_{19}H_{14}N_3$: 284.1188].

Synthesis of N-methyl eudistomin U was achieved by following the procedure of Edistomin U as mentioned above and obtained in 72% yield.

N-methyl eudistomin U (**7b**). Yield: 75% yield (44 mg); ^{1}H NMR (500 MHz, DMSO−d_6) δ: 11.31 (s, 1H), 8.59 (d, J = 7.8 Hz, 1H), 8.58 (d, J = 5.2 Hz, 1H), 8.30 (s, 1H), 8.26 (s, 1H), 7.97 (d, J = 5.2 Hz, 1H), 7.72 (d, J = 8.2 Hz, 1H), 7.57 (m, 2H), 7.29 (m, 2H), 7.27 (m, 1H), 3.98 (m, 3H);^{13}C NMR (100 MHz, DMSO−d_6) δ; 153.8, 141.2, 140.5, 138.8, 137.4, 132.6, 130.6, 128.7, 128.3, 127.1, 122.9, 122.6, 121.9121.8, 120.5, 119.9, 116.1, 112.0, 110.3, 33.4; HRMS (ESI): calcd. for $C_{20}H_{15}N_3$ $[M + H]^+$ 298.1344; found 298.1340.

4.3 | Synthesis of natural product, harmane[22] (10a)

Step 1: In a 5 mL sealed tube were added a mixture of acetaldehyde (**5c**) (110 μL, 2 mmol, 10 equiv.,), tryptamine (**1c**, 32 mg, 0.20 mmol, 1 equiv.,) and *p*-toluene sulphonic acid (3.44 mg, 0.02 mmol, 0.1 equiv.,) in NMP (1 mL) and the resulting mixture was heated at 140°C under argon atmosphere for 24 h. After the reaction was complete, the reaction mixture was concentrated under reduced pressure using rotary evaporator. The crude product thus obtained was purified by flash column chromatography on silica gel using mixture of Hexane: Ethyl acetate (70:30) as eluent to obtain the product **9a** in 85% yield (31.6 mg, 0.17 mmol).

Step 2: In a 5 mL RB flask was added compound **9a** (37.2 mg, 0.20 mmol) in NMP (1 mL) and the resulting mixture was heated at 150°C under oxygen atmosphere for 24 h. After the reaction was complete, the reaction mixture was concentrated under reduced pressure using rotary evaporator. The crude product thus obtained was purified by flash column chromatography on silica gel using mixture of hexane: Ethyl acetate (70:30) as eluent to obtain the product 10a in 76% yield (30.6 mg, 0.168 mmol).

Harmane (**10a**). Yield: 84% yield (30 mg); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.64 (s, 1H), 8.24 (d, J = 5.31 Hz, 1H), 8.17 (d, J = 7.9, 1H), 7.91 (d, J = 5.3 Hz, 1H), 7.63 (d, J = 8.2 Hz, 1H), 7.22 (d, J = 7.5 Hz, 1H), 2.81 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ; 142.6, 140.9, 138.0, 135.0, 128.3, 127.4, 122.1, 121.6, 119.6, 113.1, 112.4, 20.9.

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ORCID

Baskar Baburaj https://orcid.org/0000-0002-4463-1627

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