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GREEN SYNTHESIS OF 1-ARYL-2,3,4,9-TETRAHYDRO-1*H*-β-CARBOLINES USING FE(III)-MONTMORILLONITE AND STUDY OF THEIR ANTIMICROBIAL ACTIVITY

Gajjala Raghavendra Reddy,[1] Chinta Raveendra Reddy,[2] Gopireddy Venkata Subba Reddy,[3] Pasupuleti Visweswara Rao,[4] Poola Sreelakshmi,[5] Balam Satheesh Krishna,[5] and Cirandur Suresh Reddy[5,*]

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A series of 1-aryl-2,3,4,9-tetrahydro-1*H*-β-carbolines were synthesized using green ultrasonic synthetic approach in aqueous medium via the Pictet-Spengler reaction. The condensation reaction of tryptamine and various aromatic aldehydes at 80ºC in aqueous medium produced the corresponding 1-aryl-2,3,4,9-tetrahydro-1*H*-β-carbolines by means of heterogeneous catalysis with Fe(III)-montmorillonite catalyst. The driving force for reaction feasibility in terms of the condensation of β-arylethylamine with the corresponding aldehyde followed by the ring closure reaction is the acidic nature of the Fe(III)-montmorillonite catalyst. The advantage of this methodology is high product yield and short reaction time compared to the conventional heating and microwave irradiation methods. The structures of synthesized compounds were confirmed by IR, ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry, and elemental analysis. All products were screened for their antimicrobial activity, and some compounds exhibited significant activity against selected bacteria and fungi.

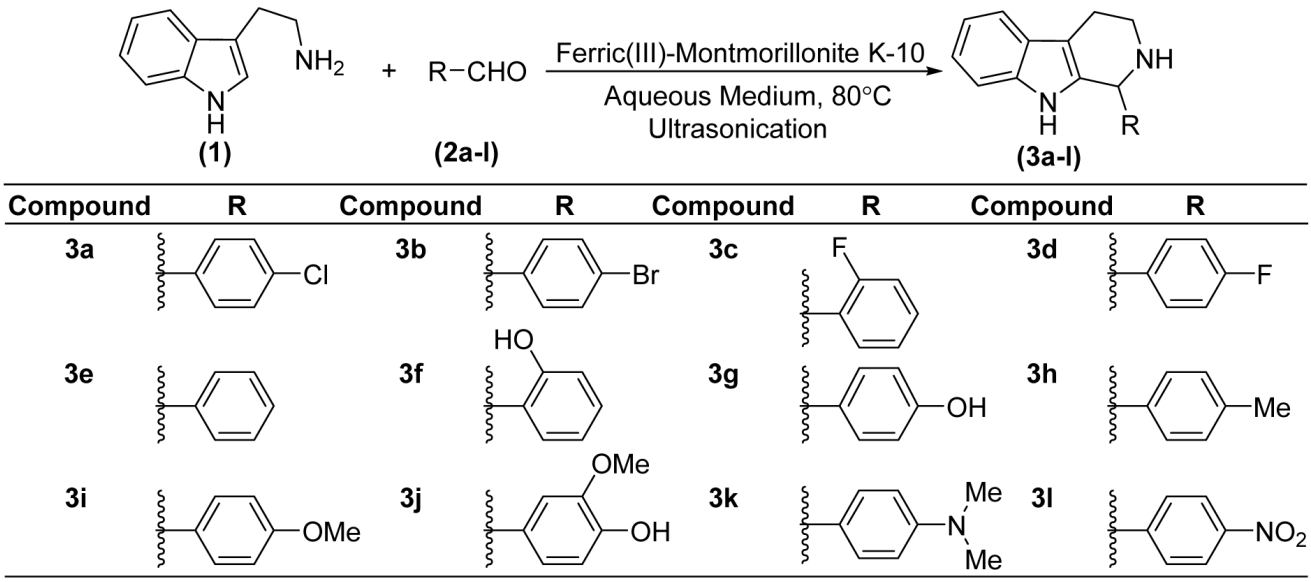
Keywords: tryptamine, Fe(III)-montmorillonite; aqueous medium; green synthesis**;** ultrasonic irradiation; 1-aryl-2,3,4,9-tetrahydro-1H-β-carbolines; antimicrobial activity.

1. INTRODUCTION

1-Aryl-2,3,4,9-tetrahydro-1H-β-carboline derivatives are indole fused piperidines containing tricyclic alkaloids found in mammalian tissues [1] and cells of plant origin [2], which possess various biological activities including anticancer, antimicrobial, antithrombotic, antimalarial, antitubercular, antileishmanial, anti-HIV and antiviral [3]. A natural tetrahydro-β-carboline alkaloid tetrahydroharman(e) has been extracted from *Guiera senegalensis*, an African plant [4]. The synthesis of this type of compounds has been achieved by the Pictet-Spengler reaction [5]. This reaction involves the condensation of an aryl ethyl amine such as tryptamine with aryl aldehydes to form the imine intermediates, which upon auto endo cyclization results in the formation of 1-aryl-2,3,4,9-tetrahydro-1*H*-β-carbolines [6]. Since the development of this reaction [7], optimization studies including catalysts, reaction conditions and starting substrates have been tried with some success. Various catalyst systems such as Bronsted acids [8], Lewis acids [9], DES [10], enzymatic [11], organocatalysts [12], RTILs [13], and microwaves [14] were successfully employed. Even though all these systems were fruitful in terms of short reaction times and good product yields, there still is a need for the development of efficient and eco-friendly methodologies.

In this connection, we have selected the acidic clay montmorillonite as catalyst for the synthesis of 1-aryl-2,3,4,9-tetrahydro-1H-β-carboline derivatives. This catalyst proved to be useful for the synthesis of important series of compounds includinbg β-acetamido ketones [15], amidoalkyl naphthols [16], γ-lactones [17], enamines [18], and por-

[1] Department of Chemistry, Jawaharlal Nehru Technological University Anantapur, Ananthapuramu – 515 002, Andhra Pradesh, India.
[2] Department of Science & Humanities, NBKR Institute of Science & Technology, Vidyanagar – 524 413, Andhra Pradesh, India.
[3] Department of Chemistry, JNTUA College of Engineering, Pulivendula - 516 390, Andhra Pradesh, India.
[4] Department of Biomedical Sciences and Therapeutics, Faculty of Medicine and Health Sciences, Universiti Malaysia Sabah, Kota Kinabalu, 88400, Sabah, Malaysia.
[5] Department of Chemistry, Sri Venkateswara University, Tirupati – 517 502, Andhra Pradesh, India.
[*] e-mail: csrsvu@gmail.com



Scheme 1. Synthesis of 1-substituted-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indoles **3a – 3l**.

phyrins [19]. Montmorillonite is a monoclinic zeolite with molecular formula $Al_2Si_4O_{10}(OH)_2 \cdot nH_2O$. This compound is useful as an efficient and versatile acid catalyst for a wide range of organic reactions[20]. Such acid-treated clays act as solid acid heterogeneous catalysts [21] containing acidic sites that are associated with interlamellar regions. The interlamellar acidic sites on the surface area are very much influenced by the addition of water and heating up to around 100°C and act as a very strong catalytic acid [22]. Hence, the aqueous mediated organic reactions are well catalyzed by the increased surface area with swelling properties. Along with pure montmorillonite, we have also prepared and investigated the effect of some transition metal ion (Sc^{3+}, Ti^{4+}, V^{3+}, Cr^{3+}, Mn^{2+}, Fe^{3+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}) paired montmorillonites as catalysts in the synthesis of 1-aryl-2,3,4,9-tetrahydro-1H-β-carbolines. The main advantage of these catalysts is that they direct product specific reactions and form the title compounds rather than forming unnecessary byproducts. Moreover, these heterogeneous catalysts can be easily removed from the reaction medium and can be reused further. Additional advantages are that these catalysts are cost-effective, strongly acidic, non-corrosive, and provide high product yield under mild operating conditions.

2. EXPERIMENTAL

2.1. Materials and Methods

Reagents and chemicals were purchased from Sigma-Aldrich, and reactions were carried out sonochemically in Power Sonic 405 micron process controlled benchtop ultrasonic reactor at 40 KHz frequency and 350 W output power. The melting points of the products were determined in open capillaries by using EZ-Melt automated melting point apparatus. The IR spectra were recorded on Bruker Alpha-Eco ATR-FTIR interferometer equipped with ZnSe crystal and presented as absorbance versus wavenumber (cm^{-1}). The NMR spectra were recorded in $CDCl_3$ on Bruker NMR spectrometer operating at 400 MHz for ^1H NMR and 100 MHz for ^{13}C NMR, and referenced to TMS internal standard. The mass spectra were measured using JEOL GCMATE II GC-MS spectrometer. Elemental analyses were carried out using Thermo Finnigan analyzer.

2.2. Chemical Synthesis

Tryptamine **(1),** 4-chlorobenzaldehyde **(2a)** and 10 mol% of Fe(III)-Mmntmorillonite K-10 were dissolved in distilled water in RB flask, and heated ultrasonically at 80°C for 2 h. The progress of reaction was monitored by thin layer chromatography (TLC). Upon completion of reaction, the mixture was extracted with ethyl acetate, dried over anhydrous sodium sulfate, and filtered. The resulting filtrate was evaporated under reduced pressure to obtain crude product (Scheme 1). Then, the product was purified by column chromatography on silica gel using ethyl acetate and hexane (1:2) mixture to obtain pure 1-(4-chlorophenyl)-2,3,4,9-tetrahydro-1H-β-carboline **(3a)** and other synthesized compounds **3b – 3l** as confirmed by spectral data and elemental analyses.

1-(4-Chlorophenyl)-2,3,4,9-tetrahydro-1*H*-β-carboline (3a): Yield: 95%; White solid; MP: 205 – 207°C; IR (ZnSe): 3297 (-NH) cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$): δ 12.45 (s, 1H), 7.40 – 7.37 (m, 3H), 7.25 – 7.04 (m, 5H), 5.26 (s, 1H), 3.95 – 3.92 (m,1H), 3.22 – 3.19 (m, 1H), 2.69 – 2.88 (m, 2H), 1.69 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.24, 136.46, 136.26, 134.76, 129.24, 128.83, 127.53, 122.12, 121.96, 119.25, 118.96, 114.04, 111.12, 107.53,

62.04, 43.44, 26.82 ppm; LCMS *m/z*: 282 (M+). Anal. calcd. for $C_{17}H_{15}ClN_2$ (%): C, 72.21; H, 5.35; N, 9.91; Found: C, 72.15; H, 5.34; N, 9.87.

1-(4-Bromophenyl)-2,3,4,9-tetrahydro-1*H*-β-carboline (3b): Yield: 88%; Yellow solid; MP: 198 – 199°C; IR (ZnSe): 3285 (-NH) cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$): δ 12.35 (s, 1H),7.54 – 7.50 (d, 2H), 7.47 – 7.33 (m, 4H), 7.25 (s, 2H), 5.53 (s, 1H), 3.28 – 3.23 (m, 2H), 2.86 – 2.81 (m, 2H), 1.75 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.27, 137.06, 134.55, 132.67, 131.49, 129.84, 127.38, 126.94, 125.76, 122.88, 120.49, 119.03, 112.26, 109.83, 58.01, 46.35, 22.46 ppm; LCMS *m/z*: 326 (M+). Anal. calcd. for $C_{17}H_{15}BrN_2$ (%): C, 62.40; H, 4.62; N, 8.56; Found: C, 62.35; H, 4.60; N, 8.53.

1-(2-Fluorophenyl)-2,3,4,9-tetrahydro-1*H*-β-carboline (3c): Yield 98%; Pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.78 (br s, 1H), 7.54 – 7.59 (m, 1H), 7.27 – 7.33 (m, 1H), 7.19 – 7.24 (m, 1H), 7.07 – 7.18 (m, 5H), 5.56 (s, 1H), 3.26 – 3.32 (m, 1H), 3.10 – 3.17 (m, 1H), 2.76 – 2.84 (m, 2H), 1.93 (br s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.6, 135.9, 132.7, 129.6, 129.4, 128.8, 127.3, 124.2, 121.7, 119.3, 118.2, 115.6, 110.7, 110.6, 50.4, 41.8, 22.6 ppm; LCMS *m/z*: 266 (M^+). Anal. calcd. for $C_{17}H_{15}FN_2$ (%): C, 76.67; H, 5.68; N, 10.52; Found: C, 76.64; H, 5.67; N, 10.49.

1-(4-Fluorophenyl)-2,3,4,9-tetrahydro-1*H*-β-carboline (3d): Yield: 89%; Pale yellow solid; MP: 183 – 188°C; IR (ZnSe): 3346 (-NH) cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$): δ 12.43 (s, 1H), 7.47 – 7.41 (m, 4H), 7.25 – 7.19 (d, 2H), 6.80 – 6.77 (d, 2H), 5.83 (s, 1H), 3.44 – 3.41 (m, 2H), 2.85 – 2.82 (m, 2H), 1.75 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.27, 141.35, 136.60, 134.29, 130.47, 128.22, 123.15, 121.93, 120.53, 118.88, 115.04, 114.31, 112.26, 110.07, 60.85, 45.94, 22.26 ppm; LCMS *m/z*: 266 (M^+). Anal. calcd. for $C_{17}H_{15}FN_2$ (%): C, 76.67; H, 5.68; N, 10.52; Found: C, 76.62; H, 5.67; N, 10.48.

1-Phenyl-2,3,4,9-tetrahydro-1*H*-β-carboline (3e): Yield: 93%; White solid; mp 206 – 207°C; IR (ZnSe): 3290 (-NH) cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$): δ 12.45 (s, 1H), 7.42 – 7.36 (m, 4H), 7.23 – 7.05 (m, 5H), 5.26 (s, 1H), 3.96 – 3.93 (m, 1H), 3.22 – 3.19 (m, 1H), 2.65 – 2.83 (m, 2H), 1.64 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.28, 136.48, 136.26, 134.74, 129.23, 128.45, 127.56, 122.34, 121.95, 119.19, 118.92, 114.12, 111.22, 107.52, 62.08, 43.41, 26.76 ppm; LCMS *m/z*: 248 (M^+). Anal. calcd. for $C_{17}H_{16}N_2$ (%): C, 82.22; H, 6.49; N, 11.28; Found: C, 81.26; H, 6.34; N, 11.25.

2-(2,3,4,9-Tetrahydro-1*H*-β-carbolin-1-yl)phenol (3f): Yield: 84%; Yellow solid; MP: 213 – 214°C; IR (ZnSe): 3277 (-NH) cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$): δ 12.65 (s, 1H), 7.83 – 7.79 (m, 4H), 7.63 (s, 1H), 7.44 (s, 1H), 6.95 (s, 1H), 6.88 (s, 1H), 5.43 (s, 1H), 3.96 (s, 1H), 3.08 – 3.04 (m, 2H), 2.85 – 2.80 (m, 2H), 1.89 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.47, 138.53, 134.67, 131.03, 130.44, 127.83, 126.36, 122.35, 120.28, 119.67, 118.84, 118.45, 111.55, 108.26, 56.67, 45.23, 20.84 ppm; LCMS *m/z*: 264 (M^+). Anal. calcd. for $C_{17}H_{16}N_2O$ (%): C, 77.25; H, 6.10; N, 10.06; Found: C, 77.21; H, 6.09; N, 10.04.

4-(2,3,4,9-Tetrahydro-1*H*-β-carbolin-1-yl)phenol (3g): Yield: 89%; Pale yellow solid; MP: 191–193°C; IR (ZnSe): 3318 (-NH) cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$): δ 12.36 (s, 1H), 7.95 (d, 2H), 7.35 (d, 2H), 6.95 – 6.91 (m, 4H), 5.43 (s, 1H), 4.23 (s, 1H), 3.05 – 3.03 (m, 2H), 2.88 – 2.87 (m, 2H), 1.93 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.36, 140.87, 136.54, 132.46, 130.62, 127.44, 121.37, 120.45, 118.44, 115.74, 110.27, 108.36, 60.14, 45.25, 22.07 ppm; LCMS *m/z*: 264 (M^+). Anal. calcd. for $C_{17}H_{16}N_2O$ (%): C, 77.25; H, 6.10; N, 10.60; Found: C, 77.20; H, 6.08; N, 10.56.

1-(p-Tolyl)-2,3,4,9-tetrahydro-1*H*-β-carboline (3h): Yield: 89%; Pale yellow solid; MP: 135 – 137°C; IR (ZnSe): 3344 (-NH) cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$): δ 12.25 (s, 1H), 7.57 – 7.52 (m, 2H), 7.46 – 7.39 (m, 3H), 7.33 – 7.26 (m, 3H), 12.25 (s, 1H), 5.36 (s, 1H), 3.44 – 3.40 (m, 2H), 3.23 – 3.19 (m, 2H), 2.44 (d, 2H), 2.29 (s, 1H) 1.92 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.43, 137.58, 136.24, 134.14, 130.46, 129.35, 126.75, 122.83, 120.25, 116.47, 113.55, 108.44, 64.29, 51.13, 22.80, 21.52 ppm; LCMS *m/z*: 262 (M^+). Anal. calcd. for $C_{18}H_{18}N_2$ (%): C, 82.41; H, 6.92; N, 10.68; Found: C, 82.34; H, 6.89; N, 10.64.

1-(4-Methoxyphenyl)-2,3,4,9-tetrahydro-1*H*-β-carboline (3i): Yield: 91%; Pale yellow solid; MP: 204 – 206 °C; IR (ZnSe): 3296 (-NH) cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$): δ 12.45 (s, 1H), 8.12 (d, 2H), 7.53 (d, 2H), 6.91 – 7.34 (m, 4H), 5.42 (s, 1H), 3.87 (s, 3H), 3.34 (m, 1H), 3.09 (m, 1H), 2.65 – 2.87 (m, 2H), 1.98 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.49, 136.58, 134.97, 132.29, 130.04, 127.56, 121.84, 120.55, 118.35, 113.93, 111.24, 109.18, 62.23, 55.96, 45.27, 22.05 ppm; LCMS *m/z*: 278(M^+). Anal. calcd. for $C_{18}H_{18}N_2O$ (%): C, 77.67; H, 6.52; N, 10.06; Found: C, 77.62; H, 6.49; N, 10.04.

2-Methoxy-4-(2,3,4,9-tetrahydro-1*H*-β-carbolin-1-yl)-phenol (3j): Yield: 85%; Yellow solid; MP: 185 – 186°C; IR (ZnSe): 3335 (-NH) cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$): δ 12.36 (s, 1H), 7.83 – 7.79 (m, 3H), 7.64 (s, 1H), 7.45 (s, 1H), 7.25 (s, 1H), 7.04 (s, 1H), 5.27 (s, 1H), 4.26 – 4.21 (m,1H), 3.95 (s, 3H), 3.13 – 3.08 (m, 2H), 2.65 – 2.60 (m, 2H), 1.99 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.41, 145.52, 138.44, 136.23, 133.35, 128.07, 121.86, 120.99, 119.18, 118.80, 117.32, 116.23, 112.35, 109.71, 62.24, 56.83, 43.42, 22.75 ppm; LCMS *m/z*: 294(M^+). Anal. calcd. for $C_{18}H_{18}N_2O_2$ (%): C, 73.45; H, 6.16; N, 9.52; Found: C, 73.39; H, 6.13; N, 9.49.

N,N-Dimethyl-4-(2,3,4,9-tetrahydro-1*H*-β-carbolin-1-yl)aniline (3k): Yield: 87%; Yellow solid; MP: 204 – 205°C; IR (ZnSe): 3359 (-NH) cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$): δ 12.38 (s, 1H), 7.76 (d, 2H),7.25 (d, 2H), 6.85 – 6.81 (m, 4H), 5.65 (s, 1H), 3.44 – 3.40 (m, 2H), 3.25 (s, 6H), 2.71 – 2.68 (m, 2H), 2.03 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ

TABLE 1. Catalyst Optimization for Synthesis of Compound **3a**

Sample No.	Catalyst	Metal source	Reaction time (h)	Yield (%)
1	Montmorillonite	Not applicable	15	73
2	Sc^{3+}-Montmorillonite	$ScCl_3 \cdot 6H_2O$	15	81
3	Ti^{4+}-Montmorillonite	$TiCl_4$	14	77
4	V^{3+}-Montmorillonite	VCl_3	15	80
5	Cr^{3+}-Montmorillonite	$CrCl_3 \cdot 6H_2O$	15	81
6	Mn^{2+}-Montmorillonite	$MnCl_2 \cdot 4H_2O$	15	80
7	**Fe^{3+}-Montmorillonite**	**$FeCl_3 \cdot 6H_2O$**	12	85
8	Co^{2+}-Montmorillonite	$CoCl_2 \cdot 6H_2O$	15	76
9	Ni^{2+}-Montmorillonite	$NiCl_2 \cdot 6H_2O$	14	81
10	Cu^{2+}-Montmorillonite	$CuCl_2 \cdot 2H_2O$	13	82
11	Zn^{2+}-Montmorillonite	$ZnCl_2$	15	79

152.25, 138.66, 135.27, 132.03, 128.24, 127.85, 122.35, 120.43, 118.57, 112.74, 111.46, 108.03, 60.24, 44.57, 40.07, 22.85 ppm; LCMS *m/z*: 291(M^+). Anal. calcd. for $C_{19}H_{21}N_3$ (%): C, 78.32; H, 7.26; N, 14.42; Found: C, 78.26; H, 7.24; N, 14.38.

1-(4-Nitrophenyl)-2,3,4,9-tetrahydro-1*H*-β-carboline (3l): Yield: 95%; Yellow solid; MP: 172 – 173°C; IR (ZnSe): 3308 (-NH) cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$): δ 12.26 (s, 1H), 8.33 (m, 2H), 7.54 (m, 1H), 7.33 – 7.28 (m, 4H), 5.45 (s, 1H), 3.45 – 3.39 (m, 2H), 2.93 – 2.87 (m, 2H), 1.96 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.85, 145.47, 136.23, 134.17, 128.24, 123.56, 120.57, 118.95, 110.24, 109.63, 62.27, 46.43, 24.25 ppm; LCMS *m/z*: 293(M^+). Anal. calcd. for $C_{17}H_{15}N_3O_2$ (%): C, 69.61; H, 5.15; N, 14.33; Found: C, 69.59; H, 5.14; N, 14.30.

2.3. Antimicrobial Activity Assay

The antimicrobial activity of compounds **3a – 3l** against bacteria *Escherichia coli* (*E. coli*) and *Staphylococcus aureus* (*S. aureus*) and fungi *Aspergillus niger* (*A. niger*) and *Helminthosporium oryzae* (*H. oryzae*) was tested by disc diffusion and agar dilution methods, respectively. The bacterial microorganisms were cultured on nutrient broth at 37°C and fungal microorganisms were cultured on potato dextrose agar at 28°C for 18 – 24 h. The microbial growth inhibition was evaluated and compared to standard bactericide penicillin and standard fungicide griseofulvin at three concentrations (100, 50, 25 ppm) [23, 24].

TABLE 2. Optimization of Catalyst Concentration for Synthesis of Compound **3a**

Sample No.	Catalyst (mol %)	Time (h)	Yield (%)
1	1.0	12	60
2	2.5	12	64
3	5.0	12	67
4	7.5	12	70
5	10.0	12	85
6	12.5	12	75
7	15.0	12	74

3. RESULTS AND DISCUSSION

3.1. Chemistry

Experimental conditions for the synthesis of 1-aryl-2,3,4,9-tetrahydro-1*H*-β-carbolines **(3a – 3l)** from tryptamine **(1)** and substituted benzaldehydes **(2a – 2l)** were standardized with illustrative reaction of tryptamine **(1)** and 4-chloro benzaldehyde **(2a)** with respect to variable reaction conditions including catalyst selection, concentration, effective reaction temperature, energizing the reaction with conventional heating, microwave irradiation and ultrasonication.

Synthesis of metal ion exchanged montmorillonites. Montmorillonite was purchased from Sigma-Aldrich, and then transition metal ion-exchanged montmorillonites were prepared by thorough mixing of montmorillonite with aqueous solutions of selected metal salts for 4 h at room temperature, with subsequent filtration. The solid product was washed repeatedly with deionized water, dried under vacuum at room temperature to retain their surface properties intact, and ground to get fine powder [25].

Optimization of catalyst. The effective catalyst was optimized by microwave synthesis of **3a** in aqueous medium by screening the efficacy of initial montmorillonite and some of ion-exchanged derivatives paired with transition metal cations (Table 1).

The Lewis acidic strength of these catalysts grows with increase in the charge to radius ratio of exchanged cation and followed trends of the Ahrland-Chatt-Davies (ACD) and Pearson's hard and soft acid classification of metal ions in the acidity and turnover of the catalytic activity. In comparison, the yield of compound **3a** obtained using montmorillonite paired class A metal ions (Sc^{3+}, Ti^{4+}, V^{3+}, Cr^{3+}, Fe^{3+})

is higher compared to montmorillonite paired with borderline metal ions (Mn^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}), which is also higher than the yield obtained with pure montmorillonite. Hence, Fe(III)-montmorillonite catalyst produced compound **3a** in higher yields and was currently identified as catalyst of interest.

Optimization of catalyst concentration. In developing Fe(III)-montmorillonite catalyst, we have optimized its concentration using microwave synthesis of **3a** loaded with 1.0, 2.5, 5.0, 7.5, 10.0, 12.5, and 15.0 mol% of catalyst under otherwise the same reaction conditions described above and obtained 60, 64, 67, 70, 85, 75 and 74% yield, respectively (Table 2). Hence, 10 mol % is identified as effective concentration to produce **3a** in good yield, as no further improvement was observed at higher concentration (12.5 and 15.0%).

Method optimization. After selection and optimization of the concentration of Fe(III)-montmorillonite catalyst, we have checked the effect of energizing the reaction in different modes including the conventional heating, microwave irradiation and ultrasonication. It was established that the reaction with Fe(III)-montmorillonite catalyst produced the title compounds without any byproducts by conventional heating method. The better product yields were obtained under microwave irradiation conditions. However, ultrasonication of the reaction produced title compounds in higher yields as compared to the other two methods. The results of this investigation are summarized in Table 3**.** Hence, ultrasonication is identified as the best mode of energy supply for promoting this reaction.

Optimization of the reaction temperature for synthesis of compound 3a. We have optimized the reaction temperature at which the substrates are converted completely to products in high yields. We have studied the ultrasonicated reaction at seven different temperatures in the range of 60 – 90°C as shown in Table 4. The effective temperature was found to be 80°C for synthesis of compound **3a** in good yield at short reaction times.

As the ultrasonic synthesis of compounds **3a – 3l** from **1** and **2a – 2l** (containing both electron-withdrawing and electron-donating substituents) under catalytic action of Fe(III)-montmorillonite has been found effective, a deeper understanding of the reaction mechanism is an important task to discuss herein. As the reaction seems to be a classic example of Schiff base formation from primary amines and aldehyde, the hypothesis of extended possibility derived from Schiff bases of aryl substituted ethanamines to generate tetrahydro-β-carbolines via 6-endo cyclization has been paved the way for their successful synthesis. Here the transition state energy of the intermediate has also enables it to produce stable Pictet-Spengler products either simply staying as *N*-(2-arylethyl) Schiff bases or forming unwanted by-products [26]. In this context, tryptamine and aldehyde will get condensed to produce imine, which on cyclization by α-carbon attack on imino carbon (6-endo cyclization) generates tetrahydro-β-carbolines. Here, Fe(III)-montmorillonite catalyst makes Fe(III) ion and carbonyl oxygen of substrate to bound electrostatically and promotes the reaction to form an imine. Similarly, Fe(III) ion and imine were also bound electrostatically and facilitated the 6-endo cyclization, followed by proton migration to form the title products.

3.2. Antimicrobial Activity:

Compounds **3a – 3l** were screened for their antibacterial activity against the growth of *S. aureus* (Gram positive) and *E. coli* (gram negative) at different concentrations (100, 50, 25 ppm) by disk diffusion method and were found to be effective against both bacteria with reference to Penicillin. Further, their antifungal activity was evaluated against the growth of *A. Niger* and *H. oryzae* fungi at different concentrations (100, 50, 25 ppm) with reference to griseofulvin. The results expressed in terms of the zone of inhibition (presented in Tables 5 and 6) were found consistent with respect to cultures as well as concentrations. Compounds **3b**, **3f**, **3g, 3i, 3j** and **3k** substituted with bromo, 2-hydroxy, 4-hydroxy, 4-methoxy, 2-methoxy-4-hydroxy and 4-N,N-dimethyl amino groups, respectively, are found more potent as compared to other. Theoretically, the structure – activity relationship of the above compounds shows that all groups substituted in the aforementioned active compounds are potent to inhibit the growth of test microorganisms and, hence,

TABLE 3. Optimization of Energy Source for Synthesis of Selected Compounds

Compound	Conventional heat (100°C)		Microwave radiation (90°C)		Ultrasonication (80°C)	
	Time (h)	Yield (%)	Time (h)	Yield (%)	Time (h)	Yield (%)
3a	12	75	1	85	3	96
3f	12	72	1	80	3	95
3h	12	70	1	78	3	93
3k	12	65	1	76	3	94

[a] Catalyst concentration in all reactions was 10.0 mol%

TABLE 4. Optimization of Reaction Temperature for Ultrasonic Synthesis of Compound **3a**

Sample No.	Temperature (°C)	Time (h)	Yield (%)
1	60	4	84
2	65	4	87
3	70	4	90.5
4	75	4	93
5	80	3	96
6	85	3	95.5
7	90	4	94

they have successfully improved the activity of basic 2,3,4,9-tetrahydro-1*H*-β-carboline molecule.

Compounds **3b**, **3f**, **3g, 3i, 3j** and **3k** substituted with bromo, 2-hydroxy, 4-hydroxy, 4-methoxy, 2-methoxy-4-hydroxy and 4-*N*,*N*-dimethyl amino groups, respectively, are found to effectively inhibit the growth of microbial cultures of *E. coli, S. aureus, A. niger,* and *H. oryzae* in good comparison to the standard drugs.

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TABLE 5. Antibacterial Activity (Zone of Inhibition, %) of Compounds **3a – 3l** (μg/ mL)

Compound	*Escherichia coli*			*Staphylococcus aureus*		
	100	50	25	100	50	25
3a	14.93 ± 1.25	9.06 ± 1.45	5.72 ± 1.39	15.06 ± 1.19	8.45 ± 1.13	6.27 ± 1.54
3b	19.10 ± 1.74	12.49 ± 1.665	8.64 ± 1.32	21.45 ± 1.58	13.43 ± 1.47	8.85 ± 1.18
3c	15.73 ± 1.96	7.38 ± 1.46	5.32 ± 1.25	14.47 ± 1.36	7.45 ± 1.38	5.77 ± 1.58
3d	17.91 ± 0.88	6.55 ± 1.24	5.44 ± 1.52	15.38 ± 1.44	6.36 ± 1.49	5.38 ± 0.92
3e	16.38 ± 0.98	6.43 ± 1.38	4.26 ± 1.48	13.75 ± 1.06	7.32 ± 1.07	4.54 ± 1.32
3f	20.17 ± 1.38	12.76 ± 1.23	8.83 ± 1.36	21.35 ± 0.94	12.17 ± 0.95	8.33 ± 1.47
3g	21.86 ± 1.12	11.72 ± 1.54	9.76 ± 1.24	20.25 ± 1.54	11.56 ± 0.99	9.13 ± 1.36
3h	14.54 ± 0.92	7.55 ± 1.48	4.38 ± 1.44	15.36 ± 1.44	6.76 ± 1.16	5.45 ± 1.12
3i	21.67 ± 1.11	11.75 ± 1.36	8.32 ± 1.19	19.18 ± 1.25	11.74 ± 1.17	9.38 ± 1.07
3j	19.33 ± 1.25	12.54 ± 1.41	9.47 ± 1.48	20.23 ± 1.16	13.59 ± 1.05	8.90 ± 1.25
3k	20.71 ± 1.32	12.36 ± 1.25	8.61 ± 1.29	21.34 ± 1.26	12.49 ± 1.62	8.34 ± 1.26
3l	16.27 ± 1.19	8.96 ± 1.34	5.87 ± 1.43	17.83 ± 0.99	9.38 ± 1.53	6.67 ± 1.16
Penicillin	20.68 ± 1.23	12.24 ± 1.19	8.47 ± 1.65	20.36 ± 1.16	12.27 ± 1.22	8.43 ± 0.97

TABLE 6. Antifungal Activity (Zone of Inhibition, %) of Compounds **3a – 3l** (μg/ mL)

Entry	*Aspergillus niger*			*Helminthosporium oryzae*		
	100	50	25	100	50	25
3a	14.53 ± 1.28	9.87 ± 1.44	3.78 ± 1.46	13.78 ± 1.36	7.87 ± 1.19	3.54 ± 1.74
3b	22.56 ± 1.16	12.74 ± 1.27	6.34 ± 0.87	19.57 ± 1.28	9.65 ± 1.66	5.72 ± 1.15
3c	13.52 ± 1.45	9.58 ± 1.38	3.85 ± 1.08	14.43 ± 1.44	6.72 ± 1.38	3.36 ± 1.22
3d	14.63 ± 1.15	9.32 ± 1.06	2.79 ± 1.43	13.68 ± 1.21	8.38 ± 1.28	2.89 ± 1.34
3e	14.43 ± 1.71	10.66 ± 1.36	3.27 ± 1.06	12.73 ± 1.69	7.57 ± 1.08	3.18 ± 0.98
3f	21.21 ± 1.53	11.21 ± 0.99	6.82 ± 1.19	19.77 ± 1.15	10.61 ± 1.26	6.27 ± 0.97
3g	20.45 ± 1.62	12.17 ± 1.22	6.41 ± 1.22	21.83 ± 0.95	11.74 ± 1.54	5.44 ± 0.89
3h	13.29 ± 1.44	9.78 ± 0.94	3.57 ± 1.33	14.34 ± 1.66	9.39 ± 1.45	3.58 ± 1.07
3i	19.36 ± 1.94	11.97 ± 1.17	6.67 ± 1.19	19.87 ± 1.57	11.55 ± 1.26	5.76 ± 0.96
3j	21.55 ± 1.35	12.35 ± 1.54	6.35 ± 1.28	22.43 ± 1.28	12.77 ± 1.44	6.89 ± 1.34
3k	20.76 ± 1.46	12.54 ± 1.55	7.52 ± 1.15	21.56 ± 1.18	11.56 ± 1.27	5.72 ± 1.60
3l	14.45 ± 1.38	6.12 ± 0.98	3.22 ± 1.45	15.87 ± 1.29	5.35 ± 1.35	3.57 ± 1.24
Griseofulvin	20.34 ± 0.98	10.46 ± 0.94	5.45 ± 1.08	20.35 ± 1.45	10.42 ± 1.27	5.35 ± 1.49

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest related to this article.

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