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ECO-FRIENDLY SYNTHESIS AND CHARACTERIZATION OF 3-HYDROXY-1-METHYL-4-[4-(SUBSTITUTED PYRIDIN-2-YLOXY) PHENETHYL] PYRIDIN-2(1*H*)-ONES

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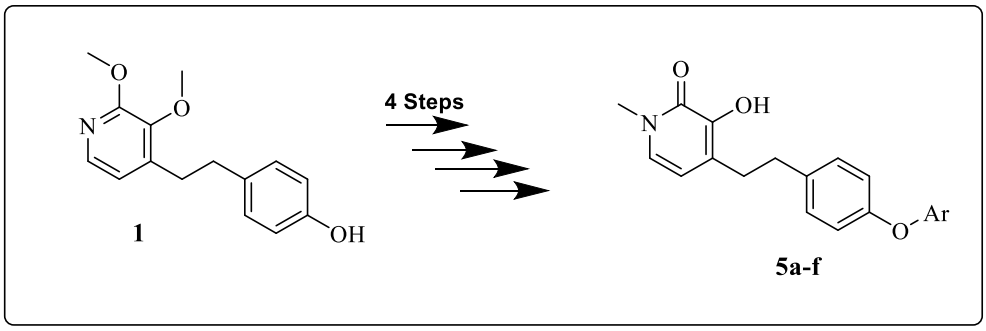
Abstract

A green strategy for the synthesis of 3-Hydroxy-1-methyl-4-[4-(substituted pyridin-2-yloxy) phenethyl]pyridin-2(1*H*)-ones in high yields with excellent purity was developed via sequential *O*-arylation, amidation, *N*-methylation and ether hydrolysis under microwave irradiation in this manuscript.

Key words: *pyridine, pyridone, pyrimidine, phenethyl, microwave irradiation (MWI).*



Graphical Abstract

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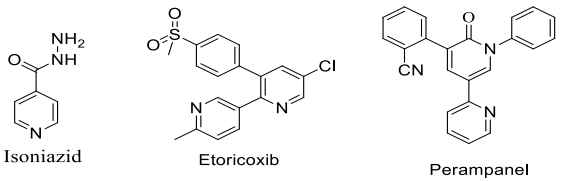
INTRODUCTION:

Pyridine scaffolds have also increasing importance for modern medicinal implementation and are expected to deliver several applications in day-to-day life. In recent years, pyridine and its derivatives have attracted a great deal of interest because of their broad pharmaceutical and industrial applications. They are reported to possess various activities such as anti-diabetic, [1] anti-fungal,[2] anti-inflammatory,[3-5] anti-microbial,6-7 antitubercular,8 anticancer, antimalarial, antioxidant, aniameboic9, anti-viral10 properties, and availability in many natural products such as vitamins, coenzymes, and alkaloids. The pyridine nucleus was found in commercially available pharmaceuticals such as isoniazid (used to treat tuberculosis), etoricoxib (used to suppress the impact of COX-2 enzymes), and perampanel (used as an antiepileptic drug-first approved by FDA in 2012). Proton-pump inhibitors using pyridine as the fundamental unit include omeprazole, rabeprazole, pantoprazole, and lansoprazole.



Microwave-mediated organic synthesis provides an easy and green alternative for the synthesis of small organic molecules.[11] The use of microwave irradiation significantly increased the reaction yield and shortened the reaction times. In this context, the use of microwave irradiation conditions stands out as an environmentally benign and powerful tool for the rapid construction of the target molecules.[12-17]

Keeping in mind, biological importance of pyridine, pyridone, pyrimidine compounds, and in continuation of our research work, we planned to construct microwave-assisted reaction for the synthesis of novel pyridone derivatives from readily available chemicals in excellent yields.

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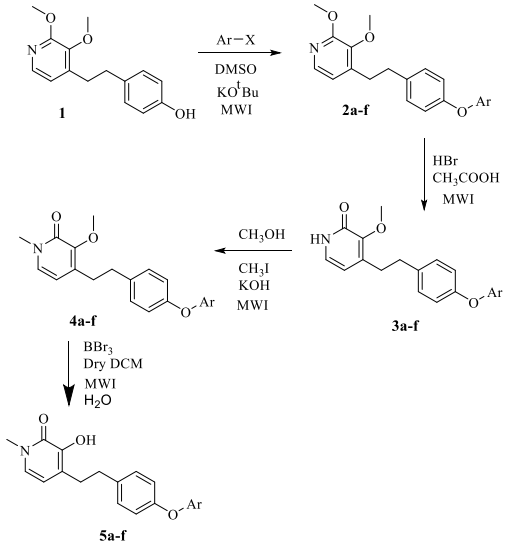
RESULTS AND DISCUSSION:

At first 4-[2-(2,3-dimethoxypyridin-4-yl)ethyl]phenol **1** was treated with substituted halopyridine using KO*t*Bu in dry DMSO under MWI conditions to furnish 2,3-dimethoxy-4-[4-(substituted pyridinyloxy)phenethyl]pyridines **2a-h**. Later the compounds **2a-h** were treated with HBr in acetic acid under MW condition to afford 3-Methoxy-4-[4-(substituted pyridinyloxy)phenethyl]pyridin-2(1*H*)-ones **3a-h**. The compounds **3a-h** were then subjected to N- methylation using KOH and methyl iodide in methanol under MWI to produce 3-methoxy-1-methyl-4-[4-(substituted pyridin-2-yloxy)phenethyl]pyridin-2(1*H*)-ones **4a-h**. Finally the key intermediates **4a-h** in dry DCM was added BBr_3 heated by MWI to obtain 3-Hydroxy-1-methyl-4-[4-(substituted pyridin-2-yloxy)phenethyl]pyridin-2(1*H*)-ones **5a-h.**The structures of the products **2-5** have been elucidated on the basis of ^{1}H NMR, IR , MS data and elemental analysis**.**



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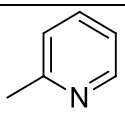
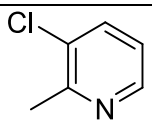
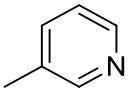
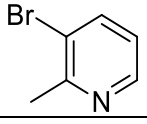
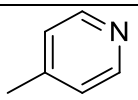
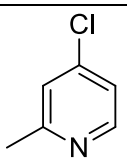
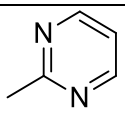
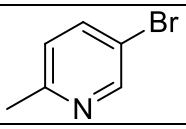
a:		**e:**	
b:		**f:**	
c:		**g:**	
d:		**h:**	

Scheme 1

EXPERIMENTAL:

Melting points were determined using a Cintex melting point apparatus and are uncorrected. Thin-layer chromatography (TLC) was performed by using Merck silica gel 60 F254 precoated plates (0.25 mm) and column chromatography was performed by using Silica gel (particle size 100-200 mesh). IR spectra (KBr) were recorded on a Perkin-Elmer BX series FTIR spectrometer. ^{1}H NMR spectra were recorded on a Bruker AMX 400 MHz spectrometer. Chemical shift values were given in ppm (δ) with TMS as an internal standard. Mass spectra were determined on Agilent LC-1100 (LC-MS) series instrument. Elemental analyses were performed on a Carlo Erba 106 and Perkin Elmer model 240 analyzers.

Synthesis of 2,3-Dimethoxy-4-[4-(substituted pyridinyloxy)phenethyl]pyridine 2a-h: To a solution of 4-[2-(2,3-dimethoxypyridin-4-yl)ethyl]phenol **1** in dry DMSO (6 mL) was added KO*t*Bu (260 mg, 2.314 mmol) and pyridine derivative and reaction mixture was subjected to MWI at 280W for 10min as indicated in **Table 1.**

Then reaction mixture was quenched with ice-cold water (30 mL), extracted with EtOAc (2x75 mL). The combined organic layers were washed with cold water (2x20 mL), brine solution, dried over Na_2SO_4 and concentrated under reduced pressure. The crude compound was purified by column chromatography (silica gel 100-200 mesh, eluted with 5-15% of EtOAc in pet ether) to afford 2,3-dimethoxy-4-[4-(substituted pyridinyloxy)phenethyl]pyridines **2a-h** in 84-92% yields.

2,3-Dimethoxy-4-[4-(pyridin-2-yloxy)phenethyl]pyridine 2a: IR (KBr) ν_{max} (cm^{-1}): 3037, 2940, 2862, 1594, 1582, 1515, 1475, 1431, 1345, 1253; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19 (dd, *J* = 1.6, 5.2 Hz, 1H), 7.79 (d, *J* = 5.2Hz, 1H), 7.69-7.65 (m, 1H), 7.22 (d, *J* = 8.4 Hz, 2H), 7.06 (d, *J* = 8.4Hz, 2H), 7.01-6.95 (m, 1H), 6.89 (d, *J* = 8.0Hz, 1H), 6.71 (d, *J* = 5.2Hz, 1H), 4.00 (s, 3H), 3.78 (s, 3H), 2.94-2.90 (m, 4H); **MS(LC-MS):** ***m/z*** 336.75 (M^+), Anal. Calcd. For $C_{20}H_{20}N_2O_3$: C, 71.41; H, 5.99; N, 8.33; Found: C, 71.53; H, 5.98; N, 8.35%.

2,3-Dimethoxy-4-[4-(pyridin-3-yloxy)phenethyl]pyridine 2b: IR (KBr) ν_{max} (cm^{-1}): 3136, 3038, 2995, 1595, 1560, 1514, 1451 1401, 1347, 1201; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33 (s, 2H), 7.77 (d, *J* = 5.2 Hz, 1H), 7.45-7.31 (m, 2H), 7.24 (d, *J* = 8.8 Hz, 2H), 7.03-6.94 (m, 2H), 6.85 (d, *J* = 5.2 Hz, 1H), 3.87 (s, 3H), 3.67 (s, 3H), 2.91-2.80 (m, 4H); **MS(LC-MS):** ***m/z*** 335.14 (M-H), Anal. Calcd. For $C_{20}H_{20}N_2O_3$: C, 71.41; H, 5.99; N, 8.33; Found: C, 71.53; H, 5.98; N, 8.35%.

2,3-Dimethoxy-4-[4-(pyridin-4-yloxy)phenethyl]pyridine 2c: IR (KBr) ν_{max} (cm^{-1}):3065, 3029, 2972, 1600, 150, 1461, 1420, 1367, 1201, 1097; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.45 (d, *J* = 4.4 Hz, 2H), 7.79 (d, *J* = 5.2 Hz, 1H), 7.23 (d, *J* = 8.8 Hz, 2H), 7.01 (d, *J* = 8.8 Hz, 2H), 6.86-6.78 (m, 2H), 6.67 (d, *J* = 5.2 Hz, 1H), 4.00 (s, 3H), 3.80 (s, 3H), 2.99-2.83 (m, 4H); **MS(LC-MS):*m/z*** 336.15 (M^+), Anal. Calcd. For $C_{20}H_{20}N_2O_3$: C, 71.41; H, 5.99; N, 8.33; Found: C, 71.53; H, 5.98; N, 8.35%.

2-{4-[2-(2,3-Dimethoxypyridin-4-yl)ethyl]phenoxy}pyrimidine 2d: IR (KBr) ν_{max} (cm^{-1}):3130, 3040, 2957, 2880, 2806, 1610, 1594, 1563, 1515, 1410, 1346, 1232; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.78 (s, 1H), 7.82 (d, *J* = 5.2 Hz, 1H), 7.72 (d, *J* = 5.2 Hz, 1H), 7.40 (d, *J* = 8.8 Hz, 2H), 7.10 (d, *J* = 8.8 Hz, 2H), 6.88-6.82 (m, 2H), 4.02 (s, 3H), 3.81 (s, 3H), 2.87-2.85 (m, 4H); **MS(LC-MS):** ***m/z*** 337.37 (M^+), Anal. Calcd. For $C_{19}H_{19}N_3O_3$: C, 67.64; H, 5.68; N, 12.46; Found: C, 67.76; H, 5.69; N, 12.48%.

4-{4-[(3-Chloropyridin-2-yl)oxy]phenethyl}-2,3-dimethoxypyridine 2e: IR (KBr) ν_{max} (cm^{-1}):3022, 1600, 1554, 1518, 1467, 1446, 1347, 1224, 1082; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, 2H), 7.31 (d, *J* = 8.8 Hz, 2H), 7.07 (d, *J* = 8.8 Hz, 2H), 6.88-6.72 (m, 2H), 6.67 (d, *J* = 5.2 Hz, 1H), 4.01 (s, 3H), 3.82 (s, 3H), 2.95-2.80 (m, 4H); **MS(LC-MS):*m/z*** 370.55 (M^+), Anal. Calcd. For $C_{20}H_{19}ClN_2O_3$: C, 64.78; H, 5.16; N, 7.55; Found: C, 64.89; H, 5.17; N, 7.58%.

4-{4-[(3-Bromopyridin-2-yl)oxy]phenethyl}-2,3-dimethoxypyridine 2f: IR (KBr) ν_{max} (cm^{-1}):3037, 2965, 2878, 2803, 1593, 1564, 1574, 1471, 1428, 1349, 1230, 1112; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (d, 2H), 7.25 (d, *J* = 8.8 Hz, 2H), 7.02 (d, *J* = 8.8 Hz, 2H), 6.77-6.71 (m, 2H), 6.64 (d, *J* = 5.2 Hz, 1H), 4.02 (s, 3H),

3.75 (s, 3H), 2.94-2.87 (m, 4H); **MS(LC-MS):*m/z*** 415.22 (M+H), Anal. Calcd. For $C_{20}H_{19}BrN_2O_3$: C, 57.84; H, 4.61; N, 19.24; Found: C, 57.89; H, 4.63; N, 19.26%.

4-{4-[(4-Chloropyridin-2-yl)oxy]phenethyl}-2,3-dimethoxypyridine 2g: IR (KBr) ν_{max} (cm^{-1}):3025, 2969, 1607, 1522, 1455, 1432, 1399, 1369, 1234, 1184, 1022; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, 2H), 7.31 (d, *J* = 8.8 Hz, 2H), 7.07 (d, *J* = 8.8 Hz, 2H), 6.88-6.72 (m, 2H), 6.67 (d, *J* = 5.2 Hz, 1H), 4.01 (s, 3H), 3.82 (s, 3H), 2.95-2.80 (m, 4H); **MS(LC-MS):*m/z*** 370.55 (M+H), Anal. Calcd. For $C_{20}H_{19}ClN_2O_3$: C, 64.78; H, 5.16; N, 7.55; Found: C, 64.87; H, 5.15; N, 7.57%.

4-{4-[(5-Bromopyridin-2-yl)oxy]phenethyl}-2,3-dimethoxypyridine 2h: IR (KBr) ν_{max} (cm^{-1}):3022, 2970, 1607, 1522, 1455, 1432, 1372, 1237, 1187, 1020; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.82 (d, *J* = 4.8 Hz, 2H), 8.41 (d, *J* = 6.8 Hz, 2H), 7.54 (d, *J* = 8.4 Hz, 2H), 7.17 (t, *J* = 4.8 Hz, 1H), 6.64 (d, *J* = 5.2 Hz, 1H), 4.01 (s, 3H), 3.74 (s, 3H), 2.90-2.85 (m, 4H); **MS(ESI): *m/z*** 414.24 (M+H), Anal. Calcd. For $C_{20}H_{19}BrN_2O_3$: C, 57.84; H, 4.61; N, 19.24; Found: C, 57.89; H, 4.63; N, 19.26%.

Table 1 - Physical data of compounds 2a-h

S. No.	Microwave method	
	Time (min)	Yield* (%)
2a	10	85%
2b	10	87%
2c	10	84%
2d	10	88%
2e	10	92%
2f	10	90%
2g	10	87%
2h	10	87%

* isolated yield after column purification

Synthesis of 3-Methoxy-4-[4-(substituted pyridinyloxy)phenethyl]pyridin-2(1H)-ones 3a-h: To 2,3-dimethoxy-4-[4-(substituted pyridinyloxy)phenethyl]pyridines **2a-h** were added HBr in acetic acid (1.5 mL). The reaction mixture was subjected to MWI at 280W for 10min as furnished in **Table 2**.

Purification of the products **3a-h** was followed by adopting same procedure of **2a-2h** to obtain 3-Methoxy-4-[4-(substituted pyridinyloxy)phenethyl]pyridin-2(1H)-ones **3a-h** in 82-91% yield.

3-Methoxy-4-(4-(pyridin-2-yloxy)phenethyl)pyridin-2(1H)-one 3a: IR(KBr) ν_{max} (cm^{-1}):3361, 3053, 2954, 2880, 2813, 2747, 1652, 1600, 1554, 1502, 1459, 1421, 1368, 1318, 1278, 1228, 1201, 1095; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.51 (s,1H), 8.32 (d, *J* = 4.4 Hz, 2H), 7.45-7.31 (m, 2H), 7.28-7.20 (m, 2H), 7.04 (d, *J* = 6.4 Hz, 1H), 6.98 (dd, *J* = 4.8 & 8.0 Hz, 2H), 6.05 (d, *J* = 6.8 Hz, 1H), 3.65 (s, 3H), 2.83-2.75 (m, 2H), 2.75-2.68 (m, 2H);**MS(LC-MS): *m/z*** 322.36 (M^+), Anal. Calcd. For $C_{19}H_{18}N_2O_3$: C, 70.79; H, 5.63; N, 8.69; Found: C, 70.85; H, 5.65; N, 8.70%.

3-Methoxy-4-[4-(pyridin-3-yloxy)phenethyl]pyridin-2(1H)-one 3b: IR(KBr) ν_{max} (cm^{-1}):3422, 3039, 2957, 2880, 2806, 1673, 1593, 1565, 1515, 1430, 1345, 1231; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.47 (s,1H), 8.11 (dd, *J* = 1.2, 4.0Hz, 1H), 7.88-7.75 (m, 1H), 7.23 (d, *J* = 8.4Hz, 2H), 7.15-6.92 (m, 5H), 6.08 (d, *J* = 6.8Hz, 1H) , 3.64 (s, 3H), 2.85-2.77 (m, 2H), 2.76-2.68 (m, 2H); **MS(LC-MS): *m/z*** 322.36 (M^+), Anal. Calcd. For $C_{19}H_{18}N_2O_3$: C, 70.79; H, 5.63; N, 8.69; Found: C, 70.85; H, 5.65; N, 8.70%.

3-Methoxy-4-[4-(pyridin-4-yloxy)phenethyl]pyridin-2(1H)-one 3c: IR(KBr) ν_{max} (cm^{-1}):3352, 3050, 2965, 2908, 1621, 1582, 1526, 1465, 1398, 1355, 1226; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.53 (s, 1H), 8.43 (d, *J* = 4.4 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 2H), 7.13-7.00 (m, 3H), 6.94-6.81 (m, 2H), 6.06 (d, *J* = 6.8 Hz, 1H), 3.66 (s, 3H), 2.88-2.78 (m, 2H), 2.77-2.59 (m, 2H); **MS(LC-MS): *m/z*** 322.36 (M^+), Anal. Calcd. For $C_{19}H_{18}N_2O_3$: C, 70.79; H, 5.63; N, 8.69; Found: C, 70.85; H, 5.65; N, 8.70%.

3-Methoxy-4-[4-(pyrimidin-2-yloxy)phenethyl]pyridin-2(1H)-one 3d: IR(KBr) ν_{max} (cm^{-1}):3272, 3176, 3045, 2980, 2897, 2815, 1660 1618, 1561, 1494, 1413, 1230, 1123; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.48 (s,1H), 8.34 (d, *J* = 4.0 Hz, 2H), 7.45-7.34 (m, 2H), 7.27-7.22 (m, 2H), 7.04 (d, *J* = 6.0 Hz, 1H), 6.45 (m, 1H), 6.05 (d, *J* = 6.8 Hz, 1H), 3.67 (s, 3H), 2.84-2.73 (m, 2H), 2.70-2.67 (m, 2H); **MS(LC-MS): *m/z*** 324.1 (M+H), Anal. Calcd. For $C_{18}H_{17}N_3O_3$: C, 66.86; H, 5.30; N, 13.00; Found: C, 66.99; H, 5.32; N, 13.03%.

4-{4-[(3-Chloropyridin-2-yl)oxy]phenethyl}-3-methoxy-1-methylpyridin-2(1H)-one 3e: IR (KBr) ν_{max} (cm^{-1}):3306, 3077, 2926, 2855, 1666, 1623, 1566, 1519, 1466, 1437, 1314, 1168, 1118; ^{1}H NMR (400 MHz, DMSO-d_6): 11.50 (s, 1H), 8.75 (d, *J* = 4.0Hz, 1H), 7.84-7.75 (m, 1H), 7.28 (d, *J* = 8.4Hz, 2H), 7.17-6.90 (m, 4H), 6.08 (d, *J* = 6.8Hz, 1H) , 3.64 (s, 3H), 2.85-2.77 (m, 2H), 2.75-2.68 (m, 2H); **MS(LC-MS): *m/z*** 355.1 (M-H), Anal. Calcd. For $C_{19}H_{17}ClN_2O_3$: C, 63.96; H, 4.80; N, 7.85; Found: C, 64.05; H, 4.81; N, 7.87%.

4-{4-([(3-Bromopyridin-2-yl)oxy]phenethyl}-3-methoxypyridin-2(1H)-one 3f: IR (KBr) ν_{max} (cm^{-1}):3352, 3050, 2965, 1663, 1621, 1582, 1526, 1465, 1398, 1335, 1226, 1118; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.45 (s, 1H), 8.21(m, 1H), 7.88-7.75 (m, 2H), 7.23 (m, 1H), 7.15-6.92 (m, 4H), 6.08 (d, *J* = 6.8Hz, 1H), 3.72 (s, 3H), 2.85-2.77 (m, 2H), 2.76-2.68 (m, 2H); **MS(LC-MS): *m/z*** 402 (M+H), Anal. Calcd. For $C_{19}H_{17}BrN_2O_3$: C, 56.87; H, 4.27; N, 6.98; Found: C, 56.99; H, 4.29; N, 6.99%.

4-{4-[(4-Chloropyridin-2-yl)oxy]phenethyl}-3-methoxy-1-methylpyridin-2(1H)-one 3g: IR (KBr) ν_{max} (cm^{-1}):3203, 3006, 2971, 2946, 1661, 1607, 1552 1511, 1430, 1370, 1266, 1221, 1117; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.41 (s, 1H), 8.11 (d, *J* = 4.2Hz, 1H), 7.87-7.73 (m, 2H), 7.21 (d, *J* = 8.4Hz, 2H), 7.15-6.92 (m, 4H), 6.08 (d, *J* = 6.8Hz, 1H) , 3.63 (s, 3H), 2.84-2.75 (m, 2H), 2.73-2.69 (m, 2H); **MS(LC-MS): *m/z*** 355.1 (M-H), Anal. Calcd. For $C_{19}H_{17}ClN_2O_3$: C, 63.96; H, 4.80; N, 7.85; Found: C, 64.05; H, 4.82; N, 7.85%.

3h: 4-{4-[(5-Bromopyridin-2-yl)oxy]phenethyl}-3-methoxypyridin-2(1H)-one 3h: IR (KBr) ν_{max} (cm^{-1}):3354, 3037, 2920, 1645, 1610, 1584, 1512, 1412, 1337, 1277, 1237, 1107; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.36 (s, 1H), 8.11 (m, 1H), 7.84-7.74 (m, 2H), 7.24 (d, *J* = 8.4Hz, 1H), 7.15-6.94 (m, 4H), 6.10 (d, *J* = 6.8Hz, 1H) , 3.64 (s, 3H), 2.83-2.74 (m, 2H), 2.72-2.64 (m, 2H); **MS(LC-MS): *m/z*** 401.25 (M+H), Anal. Calcd. For $C_{19}H_{17}BrN_2O_3$: C, 56.87; H, 4.27; N, 6.98; Found: C, 57.04; H, 4.29; N, 7.01%.

Table 2 - Physical data of compounds 3a-h

S. No.	Microwave method	
	Time (min)	Yield* (%)
3a	10	82%
3b	10	85%
3c	10	84%
3d	10	87%
3e	10	91%
3f	10	89%
3g	10	85%
3h	10	86%

* isolated yield after column purification

Synthesis of 3-Methoxy-1-methyl-4-(4-[substituted pyridinyloxy)phenethyl)pyridin-2(1H)-ones 4a-h: To a solution of 3-methoxy-4-[4-(substituted pyridin-2-yloxy)phenethyl]pyridin-2(1H)-ones **3a-h** in methanol (5 mL) were added KOH (78 mg, 1.395 mmol) and methyl iodide (0.15 ml, 2.329 mmol). The reaction mixture was exposed to MWI at 280W for 10min as furnished in **Table 3**.

Then reaction mixture was quenched with ice-cold water (30 mL), extracted with EtOAc (2x50 mL), combined organic layers were washed with water (20 mL), brine solution, dried over Na_2SO_4 and concentrated under reduced pressure to obtain 3-methoxy-1-methyl-4-[4-(substituted pyridin-2-yloxy)phenethyl)pyridin-2(1H)-ones **4a-h** in 83-93% yields.

3-Methoxy-1-methyl-4-[4-(pyridin-2-yloxy)phenethyl]pyridin-2(1H)-one 4a: IR (KBr) ν_{max} (cm^{-1}):3138, 3037, 2954, 2880, 1672, 1595, 1580, 1514, 1432, 1347, 1201, 1105; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.37-8.30 (m, 2H), 7.43-7.32 (m, 3H), 7.24 (d, *J* = 8.4 Hz, 2H), 6.98 (d, *J* = 8.4 Hz, 2H), 6.09 (d, *J* = 6.8 Hz, 1H), 3.64 (s, 3H), 3.39 (s, 3H), 2.85-2.76 (m, 2H), 2.75-2.68 (m, 2H); **MS(LC-MS): *m/z*** 337.2 (M+H), Anal. Calcd. For $C_{20}H_{20}N_2O_3$: C, 71.41; H, 5.99; N, 8.33; Found: C, 71.54; H, 6.01; N, 8.35%.

3-Methoxy-1-methyl-4-[4-(pyridin-3-yloxy)phenethyl]pyridin-2(1H)-one 4b: IR (KBr) ν_{max} (cm^{-1}):3176, 3045, 2980, 2897, 2815, 1618, 1561, 1494, 1413, 1332, 1230, 1123; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.17-8.08 (m, 1H), 7.88-7.78 (m, 1H), 7.39 (d, *J* = 6.8Hz, 1H), 7.23 (d, *J* = 8.4 Hz, 2H), 7.13-7.06 (m, 1H), 7.01 (d, *J* = 8.4 Hz, 1H), 6.97 (d, *J* = 8.4Hz, 2H), 6.15 (d, *J* = 6.8Hz, 1H), 3.65 (s, 3H), 3.39 (s, 3H), 2.85-2.78 (m, 2H), 2.77-2.69 (m, 2H); **MS(LC-MS): *m/z*** 336.38 (M^+), Anal. Calcd. For $C_{20}H_{20}N_2O_3$: C, 71.41; H, 5.99; N, 8.33; Found: C, 71.54; H, 6.01; N, 8.35%.

3-Methoxy-1-methyl-4-[4-(pyridin-4-yloxy)phenethyl]pyridin-2(1H)-one 4c: IR (KBr) ν_{max} (cm^{-1}):3037, 2954, 2880, 2806, 2750, 1603, 1594, 1584, 1515, 1429, 1346, 1231, 1112; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.44 (d, *J* = 4.4 Hz, 2H), 7.39 (d, *J* = 6.8 Hz, 1H), 7.31 (d, *J* = 8.4 Hz, 2H), 7.09 (d, *J* = 8.4 Hz, 2H), 6.92-6.84 (m, 3H), 3.66 (s, 3H), 3.40 (s, 3H), 2.88-2.78 (m, 2H), 2.77-2.70 (m, 2H); **MS(LC-MS): *m/z*** 336.38 (M+H), Anal. Calcd. For $C_{20}H_{20}N_2O_3$: C, 71.41; H, 5.99; N, 8.33; Found: C, 71.51; H, 6.00; N, 8.34%.

3-Methoxy-1-methyl-4-[4-(pyrimidin-2-yloxy)phenethyl]pyridin-2(1H)-one 4d: IR (KBr) ν_{max} (cm^{-1}):3039, 2955, 2806, 1673, 1594, 1564, 1515, 1429, 1346, 1318, 1231, 1112; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.87 (d, *J* = 4.8 Hz, 2H), 8.29 (d, *J* = 8.0 Hz, 2H), 7.77 (d, *J* = 5.2 Hz, 1H), 7.40 (t, *J* = 4.8 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 2H), 6.87 (d, *J* = 5.2 Hz, 1H), 3.86 (s, 3H), 3.67 (s, 3H), 2.91 (s, 4H); **MS(LC-MS): *m/z*** 338.28 (M+H), Anal. Calcd. For $C_{19}H_{19}N_3O_3$: C, 67.64; H, 5.68; N, 12.46; Found: C, 67.72; H, 5.69; N, 12.49%.

4-{4-[(3-Chloropyridin-2-yl)oxy]phenethyl}-3-methoxypyridin-2(1H)-one 4e : IR (KBr) ν_{max} (cm^{-1}):3029, 2968, 2887, 1659, 1605, 1566, 1512, 1458, 1424, 1367, 1228, 1177, 1115; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.72 (s, 1H), 8.35 (d, *J* = 4.0 Hz, 2H), 7.45-7.35 (m, 3H), 7.25 (d, *J* = 8.4 Hz, 2H), 7.08(d, *J* = 7.2 Hz, 1H), 6.89 (d, *J* = 8.4 Hz, 1H), 3.56 (s, 3H), 3.40 (s, 3H), 2.85-2.75 (m, 2H), 2.84-2.63 (m, 2H); **MS(LC-MS): *m/z*** 371.83 (M+H), Anal. Calcd. For $C_{20}H_{19}ClN_2O_3$: C, 64.78; H, 5.16; N, 7.55; Found: C, 64.89; H, 5.17; N, 7.58%.

4-{4-[(3-Bromopyridin-2-yl)oxy]phenethyl}-3-methoxy-1-methylpyridin-2(1H)-one 4f: IR (KBr) ν_{max} (cm^{-1}):3035, 2966, 2804, 1740, 1673, 1594, 1584, 1514, 1427, 1345, 1230, 1112; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.85 (d, *J* = 4.8 Hz, 2H), 8.32 (d, *J* = 8.0 Hz, 2H), 7.72 (d, *J* = 5.2 Hz, 1H), 7.45-7.40 (m, 2H), 7.32 (d, *J* = 8.0 Hz, 1H), 6.88 (d, *J* = 5.2 Hz, 1H), 3.87 (s, 3H), 3.65 (s, 3H), 2.93 (s, 4H); **MS(LC-MS): *m/z*** 416.12 (M+H), Anal. Calcd. For $C_{20}H_{19}BrN_2O_3$: C, 57.84; H, 4.61; N, 6.75; Found: C, 57.98; H, 4.63; N, 6.77%.

4-{4-[(4-Chloropyridin-2-yl)oxy]phenethyl}-3-methoxypyridin-2(1H)-one 4g: IR (KBr) ν_{max} (cm^{-1}):3041, 2928, 2845, 1691, 1609, 1549, 1514, 1448, 1371, 1302, 1249, 1177,1026; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.38-8.33 (m, 1H), 7.43-7.33 (m, 3H), 7.28 (d, *J* = 8.4 Hz, 2H), 6.92 (d, *J* = 8.4 Hz, 2H), 6.12 (d, *J* = 6.8 Hz, 1H), 3.65 (s, 3H), 3.35 (s, 3H), 2.87-2.74 (m, 2H), 2.72-2.68 (m, 2H); **MS(LC-MS): *m/z*** 371.83 (M+H), Anal. Calcd. For $C_{20}H_{19}ClN_2O_3$: C, 64.78; H, 5.16; N, 7.55; Found: C, 64.89; H, 5.17; N, 7.58%.

4-{4-[(5-Bromopyridin-2-yl)oxy]phenethyl}-3-methoxy-1-methylpyridin-2(1H)-one 4h: IR (KBr) ν_{max} (cm^{-1}): 3057, 2970, 1663, 1606, 1557, 1511, 1464, 1435, 1394, 1226, 1132, 1076; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.47 (d, *J* = 4.4 Hz, 2H), 7.35 (d, *J* = 6.8 Hz, 1H), 7.34 (d, *J* = 8.4 Hz, 2H), 7.12 (d, *J* = 8.4 Hz, 2H), 6.91-6.87 (m, 2H), 3.67 (s, 3H), 3.42 (s, 3H), 2.85-2.77 (m, 2H), 2.75-2.71 (m, 2H); **MS(LC-MS): *m/z*** 416.12 (M+H), Anal. Calcd. For $C_{20}H_{19}BrN_2O_3$: C, 57.84; H, 4.61; N, 6.75; Found: C, 57.95; H, 4.62; N, 6.76%.

Table 3 - Physical data of compounds 4a-h

S. No.	Microwave method	
	Time (min)	Yield* (%)
4a	10	84%
4b	10	83%
4c	10	86%
4d	10	88%
4e	10	93%
4f	10	89%
4g	10	86%
4h	10	88%

* isolated yield after column purification

Synthesis of 3-Hydroxy-1-methyl-4-[4-(pyridin-2-yloxy)phenethyl]pyridin-2(1H)-one 5a:To a stirred solution of 3-methoxy-1-methyl-4-(4-(pyridin-2-yloxy)phenethyl)pyridin-2(1H)-one (100 mg, 0.298 mmol) in dry DCM (5 mL) was added BBr_3 (1.0 M in DCM, 0.45 mL, 0.446 mmol) at 280W and exposed to MW for 10min. The reaction mixture was concentrated, crude compound was diluted with water. Aqueous layer was neutralized with $NaHCO_3$ solution and extracted with EtOAc (2x50 mL). The organic layer was washed with ice-cold water (3x20 mL), brine solution, dried over Na_2SO_4 and concentrated under reduced pressure to obtain 3-hydroxy-1-methyl-4-(4-(pyridin-2-yloxy)phenethyl)pyridin-2(1H)-one as pale pink solid (90% yield). Synthesis and purification of the products **3b-h** were followed by adopting same procedure of **3a. (**83-93% yields).

3-Hydroxy-1-methyl-4-[4-(pyridin-2-yloxy)phenethyl]pyridin-2(1H)-one 5a: IR (KBr) ν_{max} (cm^{-1}):3469, 3043, 1635, 1592, 1555, 1429, 1346, 1276, 1234, 1199, 1129; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.73 (brs, 1H, D_2O-exchangable), 8.13 (dd, *J* = 1.2 Hz, 4.8Hz, 1H), 7.90-7.75 (m, 1H), 7.24 (d, *J* = 8.0Hz, 2H), 7.16-7.05 (m, 2H), 7.01 (d, *J* = 8.0Hz, 2H), 6.97 (d, *J* = 8.4Hz, 1H), 6.08 (d, *J* = 6.8 Hz, 1H), 3.44 (s, 3H), 2.87-2.78 (m, 2H), 2.77-2.68 (m, 2H); **MS(LC-MS): *m/z*** 323.1 (M+H), Anal. Calcd. For $C_{19}H_{18}N_2O_3$: C, 70.79; H, 5.63; N, 8.69; Found: C, 70.85; H, 5.65; N, 8.70%.

3-Hydroxy-1-methyl-4-[4-(pyridin-3-yloxy)phenethyl]pyridin-2(1H)-one 5b: IR (KBr) ν_{max} (cm^{-1}):3440, 3092, 3036, 2989, 2880, 2805, 1675, 1582, 1565, 1515, 1428, 1346; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.71 (s, 1H, D_2O exchangeable), 8.33 (d, *J* = 4.0 Hz, 2H), 7.45-7.31 (m, 2H), 7.25 (d, *J* = 8.4 Hz, 2H), 7.07 (d, *J* = 7.2 Hz, 1H), 6.97 (d, *J* = 8.4 Hz, 2H), 6.05 (d, *J* = 7.2 Hz, 1H), 3.43 (s, 3H), 2.85-2.75 (m, 2H), 2.84-2.63 (m, 2H); **MS(LC-MS): *m/z*** 323.3 (M+H), Anal. Calcd. For $C_{19}H_{18}N_2O_3$: C, 70.79; H, 5.63; N, 8.69; Found: C, 70.85; H, 5.65; N, 8.70%.

3-Hydroxy-1-methyl-4-[4-(pyridin-4-yloxy)phenethyl]pyridin-2(1H)-one 5c: IR (KBr) ν_{max} (cm^{-1}):3464, 3035, 2951, 2884, 2814, 2750, 1675, 1610, 1534, 1563, 1515, 1469, 1430, 1388, 1346, 1319, 1232, 1111; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.71 (s, 1H, D_2O exchangeable), 8.43 (d, *J* = 4.4 Hz, 2H), 7.31 (d, *J* = 8.4 Hz, 2H), 7.07 (d, *J* = 8.0 Hz, 3H), 6.87 (d, *J* = 5.2 Hz, 2H), 6.05 (d, *J* = 6.8 Hz, 1H), 3.44 (s, 3H), 2.89-2.78 (m, 2H), 2.77-2.67 (m, 2H); **MS(LC-MS): *m/z*** 323.1 (M+H), Anal. Calcd. For $C_{19}H_{18}N_2O_3$: C, 70.79; H, 5.63; N, 8.69; Found: C, 70.85; H, 5.65; N, 8.70%.

3-Hydroxy-1-methyl-4-[4-(pyrimidin-2-yloxy)phenethyl]pyridin-2(1H)-one 5d: IR (KBr) ν_{max} (cm^{-1}):3430, 3040, 2987, 2882, 1661, 1593, 1575,1515,1469, 1410, 1381, 1319, 1216; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.87 (d, *J* = 4.8 Hz, 2H), 8.61 (s, 1H, D_2O exchangeable), 8.29 (d, *J* = 8.0 Hz, 2H), 7.42-7.4 (m, 3H), 6.76 (d, *J* = 7.2 Hz, 1H), 6.02 (d, *J* = 6.8 Hz, 1H), 2.92-2.83 (m, 2H), 2.79-2.70 (m, 2H); **MS(LC-MS): *m/z*** 324.13 (M+H), Anal. Calcd. For $C_{18}H_{17}N_3O_3$: C, 66.86; H, 5.30; N, 13.00; Found: C, 66.97; H, 5.30; N, 13.01%.

4-{4-[(3-Chloropyridin-2-yl)oxy]phenethyl}-3-hydroxy-1-methylpyridin-2(1H)-one 5e: IR (KBr) ν_{max} (cm^{-1}):3336, 3026, 2916, 1614, 1583, 1525, 1478, 1386, 1282, 1230, 1112; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.88 (d, *J* = 4.8 Hz, 2H), 8.63 (s, 1H, D_2O exchangeable), 8.25 (d, *J* = 8.0 Hz, 2H), 7.43-7.40 (m, 3H), 6.75 (d, *J* = 7.2 Hz, 1H), 6.05 (d, *J* = 6.8 Hz, 1H), 2.90-2.80 (m, 2H), 2.78-2.72 (m, 2H); **MS(LC-MS): *m/z*** 357 (M+H), Anal. Calcd. For

$C_{19}H_{17}ClN_2O_3$: C, 63.96; H, 4.80; N, 7.85; Found: C, 64.01; H, 4.80; N, 7.87%.

4-{4-[(3-Bromopyridin-2-yl)oxy]phenethyl}-3-hydroxy-1-methylpyridin-2(1H)-one 5f: IR (KBr) ν_{max} (cm^{-1}):3464, 3035, 2898, 1663, 1606, 1567, 1427, 1334, 1266, 1227, 1164, 1106; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.82 (d, *J* = 4.8 Hz, 2H), 8.63 (s, 1H, D_2O exchangeable), 8.31 (d, *J* = 8.0 Hz, 2H), 7.43-7.35 (m, 3H), 6.76 (d, *J* = 7.2 Hz, 1H), 6.02 (d, *J* = 6.8 Hz, 1H), 2.92-2.83 (m, 2H), 2.79-2.70 (m, 2H); **MS(LC-MS): *m/z*** 402 (M+H), Anal. Calcd. For $C_{19}H_{17}BrN_2O_3$: C, 56.87; H, 4.27; N, 6.98; Found: C, 57.01; H, 4.29; N, 7.00%.

4-{4-[(4-Chloropyridin-2-yl)oxy]phenethyl}-3-hydroxy-1-methylpyridin-2(1H)-one 5g: IR (KBr) ν_{max} (cm^{-1}):3314, 3198, 3061, 2975, 1659, 1597, 1552, 1525, 1478, 1435; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.87 (d, *J* = 4.8 Hz, 2H), 8.61 (s, 1H, D_2O exchangeable), 8.31 (d, *J* = 8.0 Hz, 2H), 7.43-7.40 (m, 3H), 6.76 (d, *J* = 7.2 Hz, 1H), 6.04 (d, *J* = 6.8 Hz, 1H), 2.92-2.82 (m, 2H), 2.79-2.70 (m, 2H); **MS(LC-MS): *m/z*** 356 (M^+), Anal. Calcd. For $C_{19}H_{17}ClN_2O_3$: C, 63.96; H, 4.80; N, 7.85; Found: C, 64.01; H, 4.81; N, 7.86%.

4-{4-[(5-Bromopyridin-2-yl)oxy]phenethyl}-3-hydroxy-1-methylpyridin-2(1H)-one 5h: IR (KBr) ν_{max} (cm^{-1}):3355, 3058, 2970, 2864, 1695, 1603, 1580, 1531, 1470, 1422, 1284, 1229, 1185, 1138, 1045; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.87 (d, *J* = 4.8 Hz, 2H), 8.61 (s, 1H, D_2O exchangeable), 8.25 (d, *J* = 8.0 Hz, 2H), 7.45-7.41 (m, 3H), 6.74 (d, *J* = 7.2 Hz, 1H), 6.05 (d, *J* = 6.8 Hz, 1H), 2.92-2.84 (m, 2H), 2.79-2.75 (m, 2H); **MS(LC-MS): *m/z*** 402.2 (M+H), Anal. Calcd. For $C_{19}H_{17}BrN_2O_3$: C, 56.87; H, 4.27; N, 6.98; Found: C, 57.05; H, 4.28; N, 7.02%.

Table 4 - Physical data of compounds 5a-h

S. No.	Microwave method	
	Time (min)	Yield* (%)
5a	10	90%
5b	10	87%
5c	10	86%
5d	10	89%
5e	10	92%
5f	10	90%
5g	10	89%
5h	10	88%

* isolated yield after column purification

CONCLUSION:

In the current study, we have synthesized different pyridone derivatives by non-conventional method. Results exhibited that microwave synthesis of pyridone derivatives had greater product yield and high purity. The structures of all the synthesized compounds were further confirmed by spectral techniques.

CONFLICT OF INTEREST:

The authors declare no conflict of interest, financial or otherwise.

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