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Four Step Synthesis and Characterization of 3-hydroxy-1-methyl-4-(4-(pyridin-4-yloxy) phenethyl) pyridin-2(1*H*)-one

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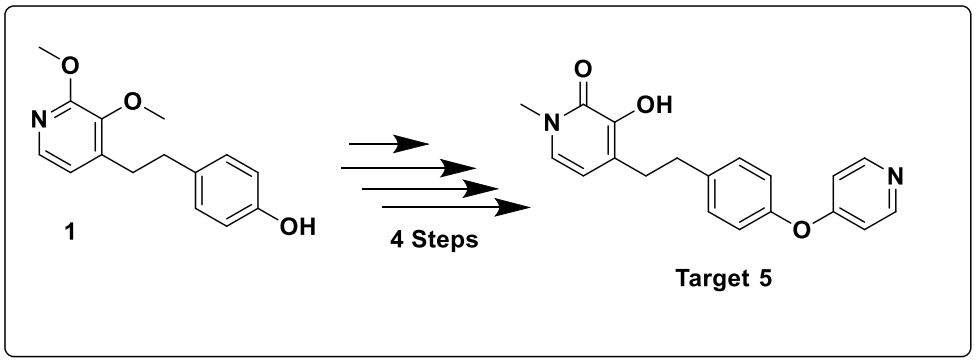
Abstract

At first a solution of 4-(2-(2,3-dimethoxypyridin-4-yl)ethyl)phenol in dry DMSO was added Cs_2CO_3 at RT. Then 4-chloropyridine hydrochloride was added and stirred at 140 ^oC for 2.5 h. The reaction mixture was quenched with ice-cold water extracted with diethyl ether to afford 2,3-dimethoxy-4-(4-(pyridin-4-yloxy)phenethyl)pyridine **2**. It is further treated with HBr in acetic acid at rt and stirred at 80 ^oC for 1.5 h to yield 3-methoxy-4-(4-(pyridin-4-yloxy)phenethyl)pyridin-2(1H)-one **3** followed by methanol were added KOH and methyl iodide at 0^oC and stirred at rt for 16 h to obtain 3-methoxy-1-methyl-4-(4-(pyridin-4-yloxy)phenethyl)pyridin-2(1H)-one **4.** It is charged with BBr_3 and stirred for 10h to obtain 3-hydroxy-1-methyl-4-(4-(pyridin-4-yloxy)phenethyl)pyridin-2(1H)-one **5** desired product with an excellent yields depicted (**Scheme I**) in this manuscript.

Key words: 2,3-dimethoxy-4-(4-(pyridin-4-yloxy)phenethyl)pyridine, BBr_3,deprotection.



Graphical Abstract

INTRODUCTION:

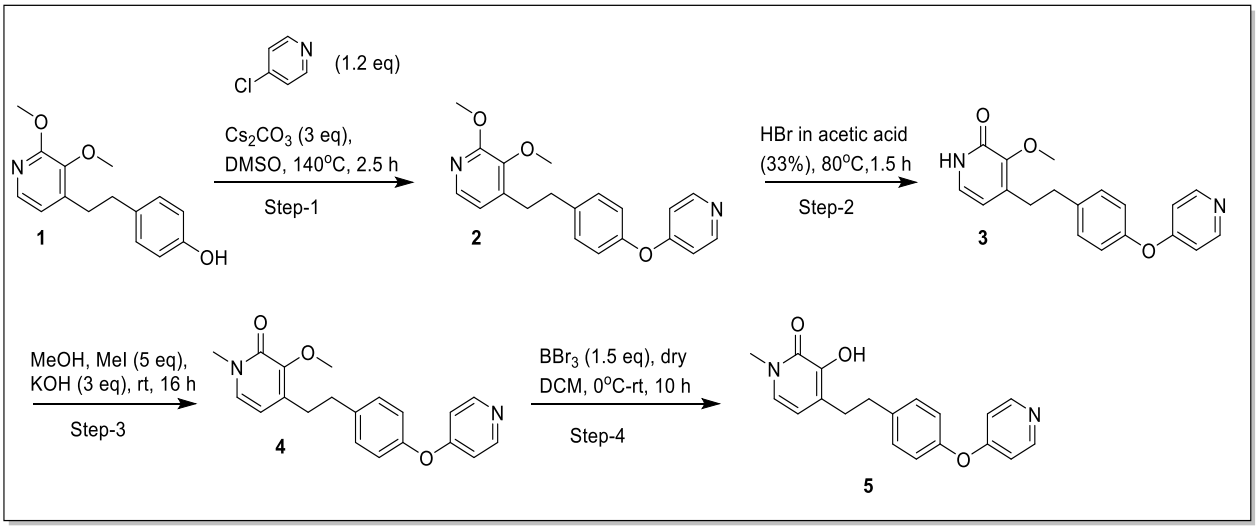
Heterocyclic moieties frequently observed in central skeletons of abundant bioactive natural alkaloids and due to its high medicinal properties, occupied a precise region in the heterocyclic field, and they have become therapeutic targets in drug discovery outlines of integral character and ability to functionalities in all three dimensions [1- 2].

The existence of molecule leads to structural rigidity and complexity and subsequently increasing its dependency on proteins [3]. Structures which makes them as core building blocks of many synthetic drugs [4-5].Synthetic targets in organic chemistry and pharmacological research fields due to their remarkable biological properties including antimicrobial [6-8], antitumor [9-12].

Herein, we have described the synthesis of 3-hydroxy-1-methyl-4-(4-(pyridin-4-yloxy) phenethyl) pyridin-2(1*H*)-one

EXPERIMENTAL:

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). ^{1}H NMR spectra were recorded on a Bruker AMX 400 MHz spectrometer.



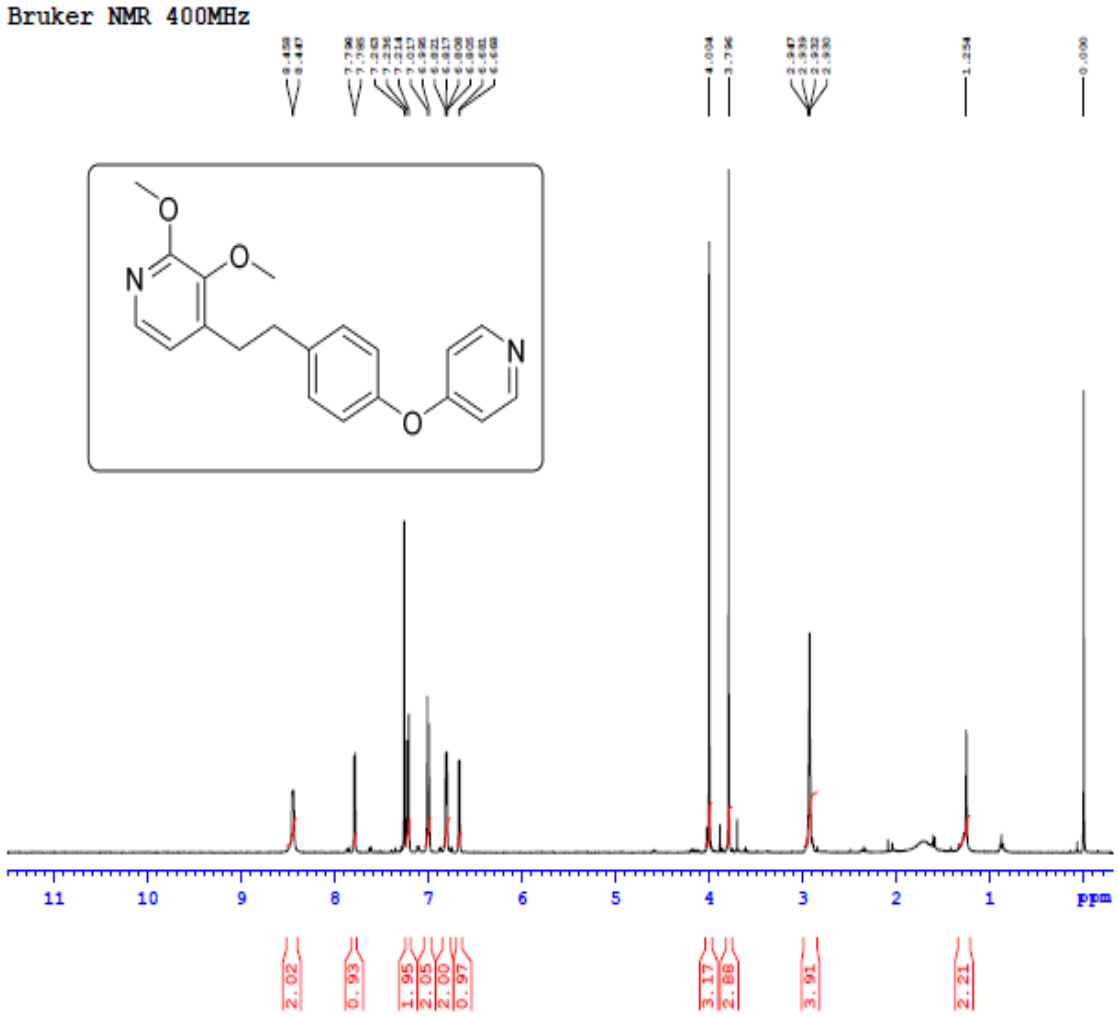
Scheme-1 Synthesis of 3-hydroxy-1-methyl-4-(4-(pyridin-4-yloxy) phenethyl)pyridin-2(1*H*)-one

RESULTS AND DISCUSSION:

Step 1: Synthesis of 2,3-dimethoxy-4-(4-(pyridin-4-yloxy)phenethyl)pyridine:

To a stirred solution of 4-(2-(2,3-dimethoxypyridin-4-yl)ethyl)phenol (200 mg, 0.722 mmol) in dry DMSO (5 mL) was added cesium carbonate (755.016 mg, 2.316 mmol) at rt and stirred at rt for 10 minutes. Then 4-chloropyridine hydrochloride (138.99 mg, 0.926 mmol) was added and stirred at 140 °C for 2.5 h. Progress of reaction was monitored by TLC. The reaction mixture was quenched with ice-cold water (30 mL), extracted with diethyl ether (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 15-40% of EtOAc in pet ether) to afford 2,3-dimethoxy-4-(4-(pyridin-4-yloxy)phenethyl)pyridine as pale yellow liquid (108 mg, 41.62% yield).

^{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).

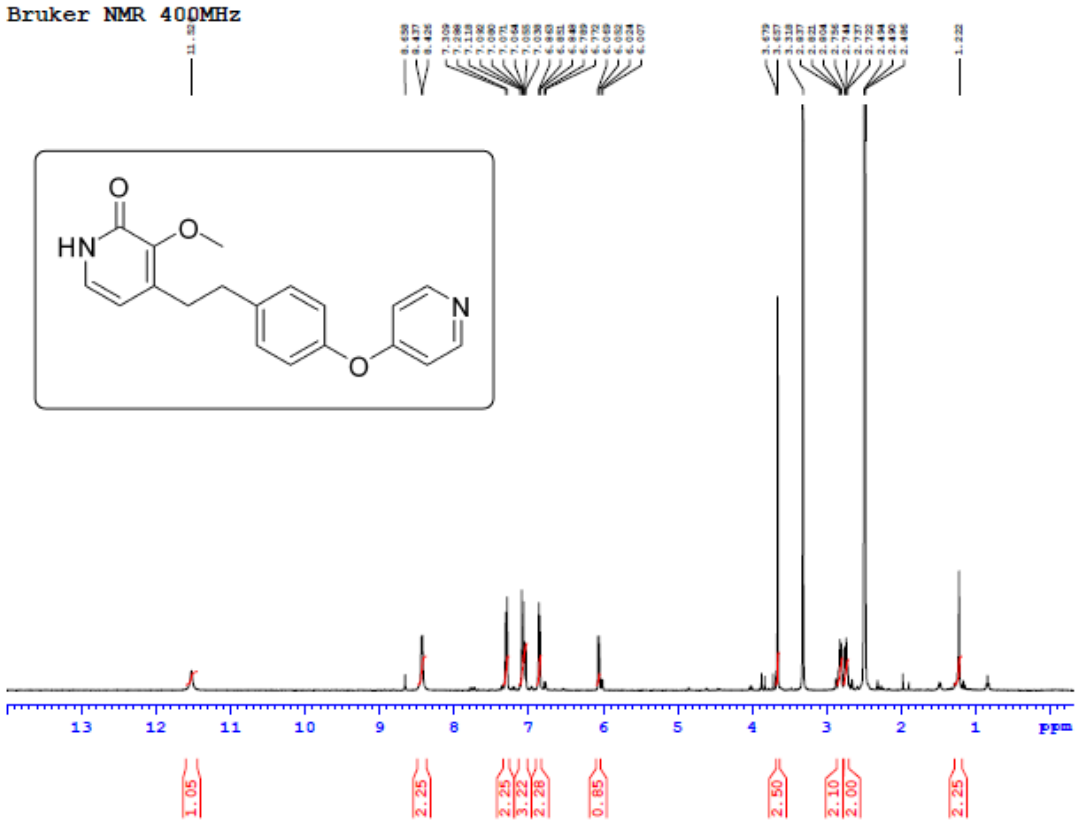


^{1}H NMR spectrum of 2,3-dimethoxy-4-(4-(pyridin-4-yloxy)phenethyl)pyridine

Step 2: Synthesis of 3-methoxy-4-(4-(pyridin-4-yloxy)phenethyl)pyridin-2(1H)-one:

To a stirred solution of 2,3-dimethoxy-4-(4-(pyridin-4-yloxy)phenethyl)pyridine (150 mg, 0.446 mmol) in HBr in acetic acid (1.5 mL) at rt and stirred at 80 ºC for 1.5 h. The progress of the reaction was monitored by TLC. The reaction mixture was quenched with ice-cold water (30 mL), basified with $NaHCO_3$ solution, 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-4-(4-(pyridin-4-yloxy)phenethyl)pyridin-2(1H)-one as pale brown gummy solid (120 mg, 83.41% yield). The crude compound was taken to next step without purification.

^{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)

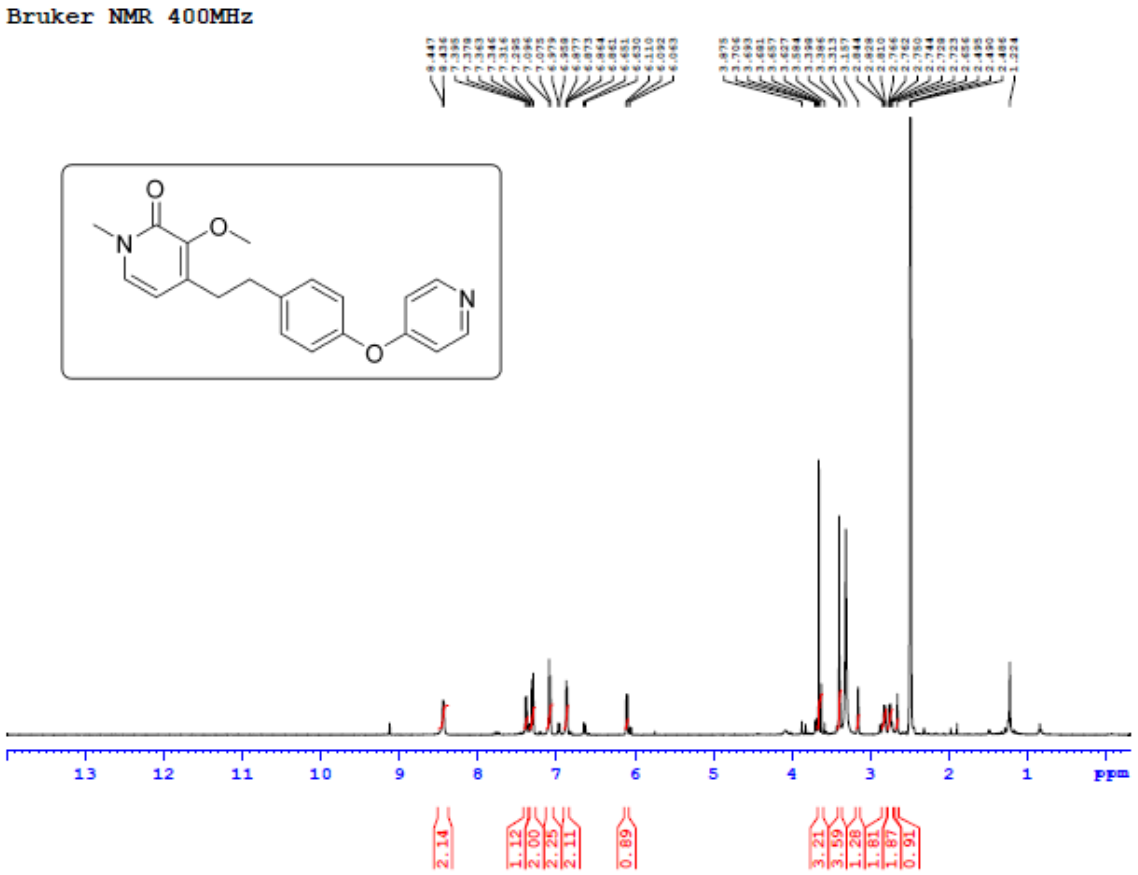


^{1}H NMR spectrum of 3-methoxy-4-(4-(pyridin-4-yloxy)phenethyl)pyridin-2(1H)-one

Step 3: Synthesis of 3-methoxy-1-methyl-4-(4-(pyridin-4-yloxy)phenethyl)pyridin-2(1H)-one:

To a stirred solution of 3-methoxy-4-(4-(pyridin-4-yloxy)phenethyl)pyridin-2(1H)-one (120 mg, 0.372 mmol) in methanol (5 mL) were added KOH (62.61 mg, 1.116 mmol) and methyl iodide (264.008 mg, 1.86 mmol) at 0 ºC and stirred at rt for 16 h. The progress of the reaction was monitored by TLC. The 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-(pyridin-4-yloxy)phenethyl)pyridin-2(1H)-one as brown gummy liquid (1.2 g, with 75% purity). Crude compound was taken to next step without purification.

^{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, 2H), 3.66 (s, 3H), 3.40 (s, 3H), 2.88-2.78 (m, 2H), 2.77-2.70 (m, 2H)

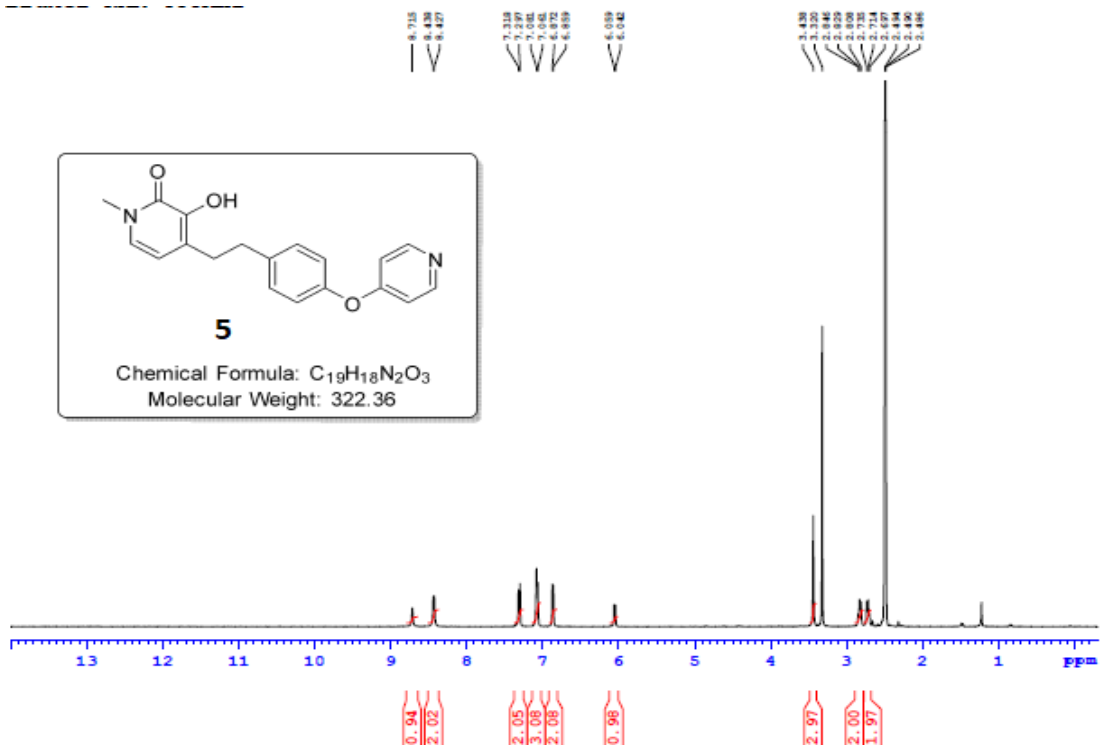


^{1}H NMR spectrum of 3-methoxy-1-methyl-4-(4-(pyridin-4-yloxy) phenethyl)pyridin-2(1H)-one

Step 4: Synthesis of 3-hydroxy-1-methyl-4-(4-(pyridin-4-yloxy) phenethyl)pyridin-2(1*H*)-one:

To a stirred solution of 3-methoxy-1-methyl-4-(4-(pyridin-4-yloxy)phenethyl)pyridin-2(1H)-one (100 mg, 0.296 mmol) in dry DCM (5 mL) were added BBr_3 (1.0 M in DCM, 0.45 mL, 0.445 mmol) at 0^{o}C and stirred at rt for 10 h. Progress of the reaction was monitored by TLC. The reaction mixture was concentrated, crude compound was diluted with water. Aqueous layer was neutralized with $NaHCO_3$ solution, then 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. The crude compound was purified by preparative TLC to obtain 3-hydroxy-1-methyl-4-(4-(pyridin-4-yloxy) phenethyl)pyridin-2(1H)-one as brown color gummy solid (35 mg, 36.52% yield).

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.71 (s, 1H), 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)



^{1}H NMR spectrum of 3-hydroxy-1-methyl-4-(4-(pyridin-4-yloxy) phenethyl)pyridin-2(1*H*)-one

CONCLUSION:

In the current study, we have synthesized 3-hydroxy-1-methyl-4-(4-(pyridin-4-yloxy) phenethyl) pyridin-2(1*H*)-one with an excellent yields and high purity.

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