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Green Synthesis of 3-(2-(4-(6-Fluorobenzo[*d*]isoxazol-3-yl)piperidin-yl) ethyl-6,7,8,9-tetrahydro-9-hydroxy-2-methylpyridol[1,2-*a*]pyrimidin-4-one

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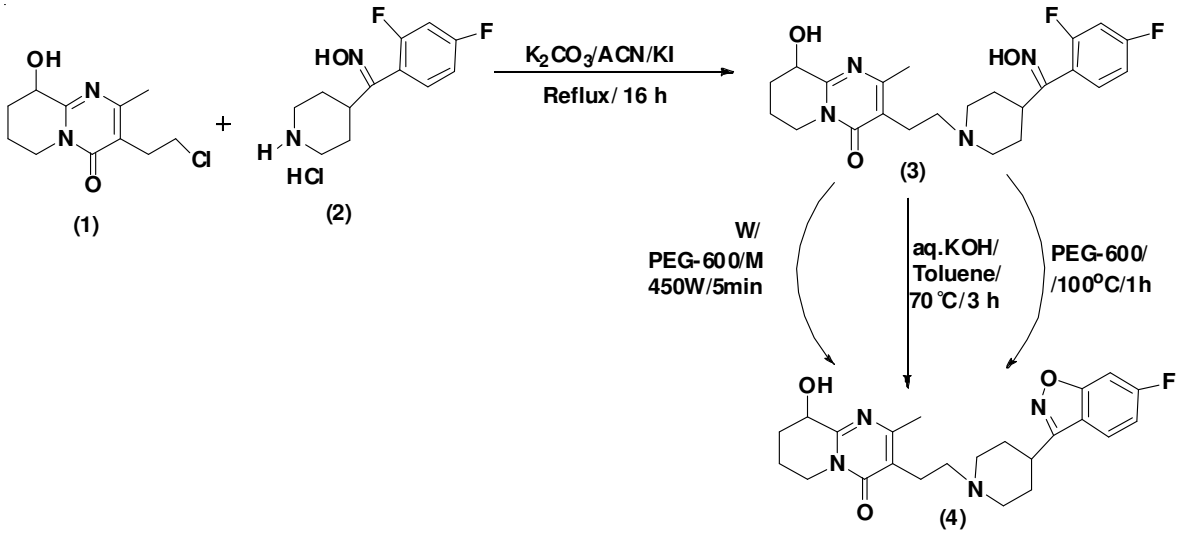
Paliperidone has been synthesized in high yields by condensation of 3-(2-chloroethyl)-9-hydroxy-2-methyl-6,7,8,9-tetrahydropyridol[1,2a]pyrimidin-4-one (**1**) and (2,4-difluoro-phenyl)-piperidin-4-yl-methanone oxime (**2**) using K_2CO_3 as a base, refluxing in acetonitrile for 16 h. The novel intermediate (**3**) underwent internal cyclization in PEG-600 as solvent yielded paliperidone (**4**). Paliperidone (**4**) from novel intermediate (**3**) has also been prepared under microwave condition using PEG-600 and also in presence of a base KOH in toluene at 70 °C for 3 h in higher yields.

Keywords: Palperidone, Antipsychotic agent, Risperidone, PEG-600, Microwave.

INTRODUCTION

Paliperidone is a typical antipsychotic agent belonging to benzisoxazole class of compounds. Paliperidone (9-hydroxy risperidone) is the major active metabolite of risperidone[1,2]. It is a second generation antipsychotic drug used for the treatment of Schizophrenia and related disorders. Low to moderate doses of the new antipsychotic paliperidone extended release (ER) were efficacious in reducing severity of global symptomatology and social impairment and in treating two specific clusters of borderline personality disorder (BPD) symptoms, like impulsive behavioural dyscontrol and cognitive-perceptual disturbance[3]. Paliperidone is a racemic mixture and chemically known as (±)-3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]6,7,8,9tetrahydro-9-hydroxy-2-methyl-4*H*-pyrido[1,2*a*]pyrimidin-4-one.

Paliperidone is a centrally active dopamine D2 and steotinergic 5-HT_{2A} antagonist, as demonstrated in both *in vitro* and *in vivo* animal and human studies. It is also active as an antagonist at α-1 and α-2 adrenergic receptors and H_1 histaminergic receptors[4].



Scheme-I

EXPERIMENTAL

Melting points are uncorrected and were determined in open capillary tubes in sulphuric acid bath. TLC was performed on silica gel-G and spotting was done using iodine or UV-light. IR spectra were recorded on a Perkin-Elmer model 446 instrument in KBr phase. ^{1}H NMR were recorded in $CDCl_3$/DMSO using 400 MHz Varian Gemini spectrometer and mass spectra were recorded on LC-MS spectrometer, model HP-5989 A.

Synthesis of 3 from 1 and 2: A mixture of 3-(2-chloroethyl)-9-hydroxy-2-methyl-6,7,8,9-tetrahy-dropyridol[1,2a]pyrimidin-4-one (**1**) (0.14 g, 10 mmol), (2,4-difluoro-phenyl)-piperidin-4-yl-methanone oxime (**2**) (0.18 g, 10 mmol) and K_2CO_3 as a mild base and KI and acetonitrile (25 mL) was refluxed for 16 h. After the completion of reaction, as shown by TLC, the mixture was filtered and dissolved the solid in dichloromethane is again filtered. Distilled out the dichloromethane and recrystallized the product with acetone.

Spectral data of 3: Yield (1.6 g, 70 %), m.p. 195-200 °C, IR (KBr, ν_{max}, cm^{-1}): 3010 (-CH=CH), 1624 (C=N), ^{1}H NMR (Fig. 1) (400 MHz, DMSO-d_6): δ 1.4-1.8 (9H, m, cyclic-$C_{1,2,17,18\&19}$-CH_2-aliphatic protons), δ 2.0 (2H, d, C_{13}-aliphatic protons), δ 2.2 (3H, s, C_9-CH_3), δ 2.4-2.5 (4H, dd, cyclic-N-$C_{16\&20}$-CH_2-aliphatic protons) δ 2.8(1H, s, C_6-OH), δ 3.4(1H, s, C_6-H-aliphatic proton), δ 3.6 (2H, d, C_{14}-aliphatic protons), δ 3.9 (1H, s, cyclic-C_3-H-aliphatic proton), δ 4.4 (1H, cyclic-C_3-H-aliphatic proton) δ 7.1-7.3 (3H, dd, aromatic), δ 10.9 (1H, s, N-OH); MS: *m/z* 447.10 (M$^+$). Anal. calcd. for $C_{23}H_{28}N_4O_3F_2$: C, 61.87; H, 6.32; F, 8.51; N, 12.55; found C,62.12; H, 6.10; F, 9.20; N, 12.50 %.

Synthesis of 4 from 3

(i) Using aq. KOH and toulene: Compound **4** (0.25 g, 10 mmol) dissolved in toluene (25 mL) and 10 mL of 30 % KOH solution is added to the mixture. The reaction mixture is heated up to 70 °C and stirred for 3 h at 70 °C. After the completion of reaction, as shown by TLC, the mixture is cooled to room temperature then the organic layer is separated and isolate with acetone to form compound **4**.

(ii) In solution phase (In PEG-600): Compound **3** (10 mM) and PEG-600 (20 mL) were heated at 100 °C on water bath for 1 h. At the end of this period, the reaction mixture was poured into ice-cold water. The separated solid was filtered, washed with water and dried. The crude products were recrystallized from suitable solvent to obtain pure **4**.

Microwave assisted method

Under microwave irradiation condition: Compound **3** (10 mM) is dissolved in PEG-600 (10 mL) and taken in a 10 mL CEM-reaction tube sealed by rubber stopper and subjected to microwave irradiation for 5 min at 450 watt in the commercial micro-wave reactor. After that, the tube was cooled and the completion of reaction was checked by TLC then poured into ice-cold water. The separated solid was filtered, washed with water and dried. The crude product was recrystallized from a suitable solvent to obtain pure **4**. For yields, Tables 1 and 2.

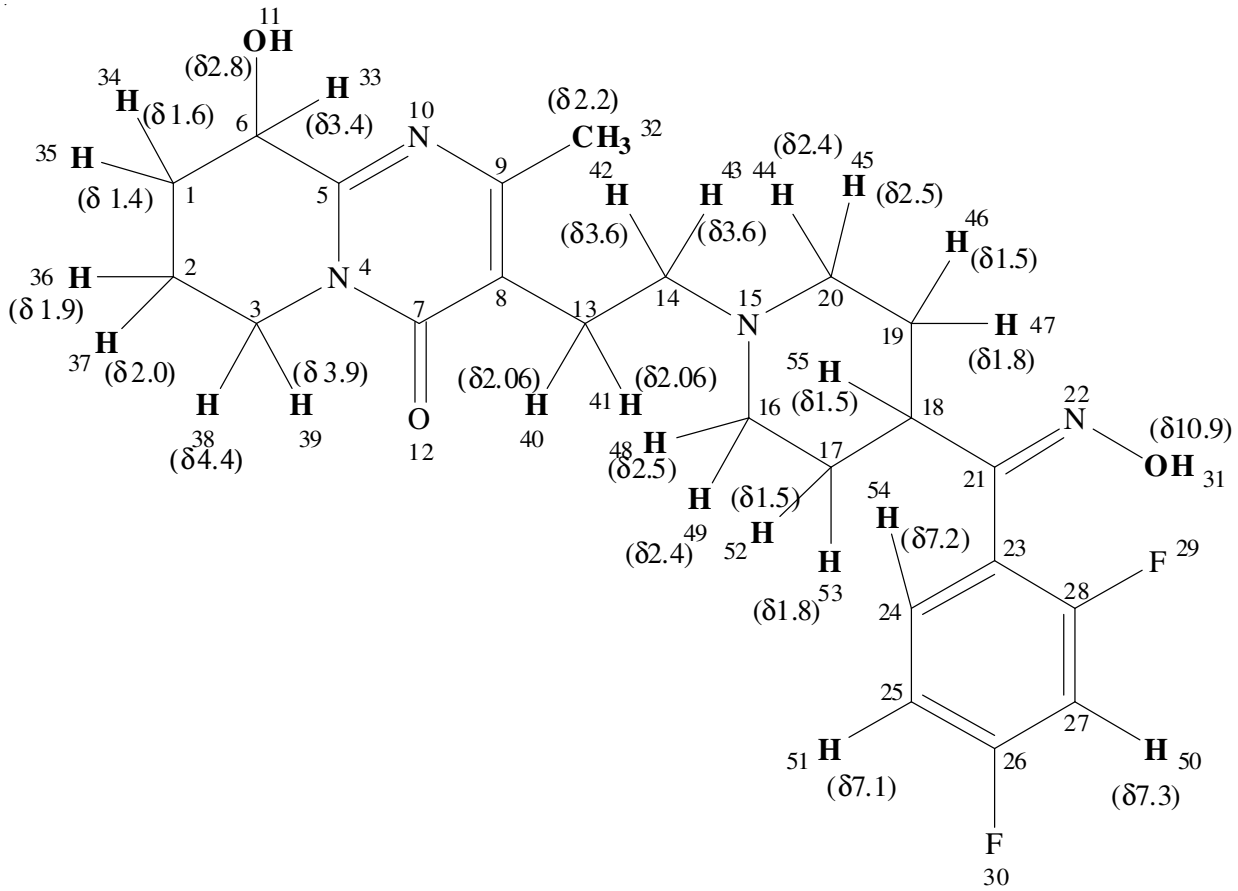


Fig. 1. ^{1}H NMR chemical shift values (δ) compound **3**

TABLE 2
COMPARITIVE YIELDS OF **4** UNDER MICROWAVE IRRADIATION AND IN SOLUTION PHASE IN VARIOUS SOLVENTS

S. No.	Solvent	Microwave irradiation			Solution phase		
		Time (min)	Temp./Watt	Yield (%)	Time (min)	Temp. (°C)	Yield (%)
1	PEG-600	10	100/450	92	60	100	90
2	Toluene	10	100/450	88	180	70	82
3	Ethanol	10	70/450	78	120	80	75
4	Glycerol	10	100/450	65	240	100	60

TABLE-1
YIELDS OF **4** IN VARIOUS SOLVENTS

S. No.	Solvent	Time (min)	Temp. (°C)	Yield (%)
1	PEG-600	60	100	90
2	Ethylene glycol	60	100	50
3	Ethanol	60	80	68
4	Ethyl lactate	60	100	55
5	Glycerol	60	100	62
6	Toulene	180	70	82

Spectral data of 4: Yield (3.6 g, 90 %), (m.p. 162-164 °C), ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.76 (ddt,1 H, 8-H), 1.89-2.04 (m, 1 H), 2.07-2.21 (m, 6 H), 2.25-2.42 (m, 2 H, CHHN of piperidine), 2.36 (s, 3 H, CH_3), 2.55 (mc, 2 H, CH_2CH_2-N), 2.79 (mc, 2 H, CH_2CH_2-N), 3.10 (mc, 1 H, CH- isoxazolyl), 3.18 (d, CHHN of piperidine), 3.87-4.03 (m, 2 H, 6-H), 4.42 (s, 1 H, OH), 4.51 (dd, 10.2 Hz, 1 H, 9-H), 7.07 (dt, 5-H of benzoisoxazole), 7.25 (dd, 7-H of benzoisoxazole), 7.72 (dd, 4-H of benzoisoxazole) ppm. FT-IR (ν_{max}, cm^{-1}) = 3287, 2934, 2783, 2754, 1616, 1535, 1413, 1338, 1269, 1183, 1143, 1130, 996, 955, 868, 853, 817, 792, 758, 698. LRMS (ESI, ion trap, 70 V): *m/z* (%) = 427 (9) $[M + H]^+$, 209 (100). $C_{23}H_{27}FN_4O_3$ (426.48): Calcd. C 64.77, H 6.38, F 4.45, N 13.14; found (sample crystallized from dimethylacetamide) C 64.84, H 6.48, F 4.49, N 13.21.

RESULTS AND DISCUSSION

Paliperidone was synthesized by known literature synthetic methods[5,6]. The another alternative synthesis of paliperidone prepared as follows:

3-(2-Chloroethyl)-9-hydroxy-2-methyl-6,7,8,9 tetrahydropyridol[1,2*a*]pyrimidin-4-one[7] (**1**) on condensation with (2,4-difluoro-phenyl)-piperidin-4-yl-methanone oxime[8] (**2**) in the presence of K_2CO_3 as a mild base and in acetonitrile as a solvent gave a novel intermediate 3-(2-{4-(2,4-difluoro-phenyl)-hydroxyimino-methyl]-piperdin-1-yl}-ethyl)-9-hydroxy-2-methyl-6,7,8,9-tetrahydro-pyrido[1,2-*a*]pyrimidin-4-one (**3**). 3 on cyclisation in basic medium and in toluene/water as a solvent gave a corresponding 3-(2-(4-(6-flurobenzo[*d*]isoxazol-3-yl)piperidin-yl)ethyl-6,7,8,9-tetrahydro-9-hydroxy-2-methylpyridol[1,2-*a*]pyrimidin-4-one (**4**).

The reaction of **4** were also carried out in PEG-600 as a solvent, both by heating at 100 °C on a water bath and in microwave method. Thus the treatment of **3** in PEG-600 at 100 °C about 1 h without using any base, followed by simple processing, gave compound **4**. Compound **4** are also synthesized in various solvents, but the better yielded by using PEG-600 (Table-1).

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