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Research Article

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Synthesis and Characterization of Impurity G of Risperidone: An Antipsychotic Drug

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ABSTRACT

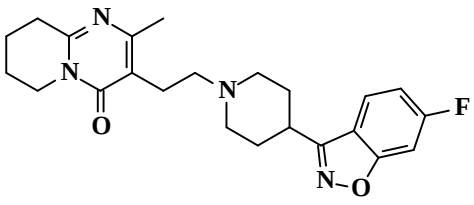
*The Metabolite and European pharmacopoeia impurity G of Risperidone, chemically known as 3-[2-[4-(4-fluoro-2-hydroxybenzoyl)piperidin-1-yl]ethyl]-2-methyl-6,7,8,9-tetrahydro-4H-pyrido -[1,2-a]pyrimidin-4-one (**2**, Risperidone hydroxy keto analogue), preparation and its structural confirmation by spectral analysis data have been described.*

Keywords: Risperidone, impurity G, hydroxy keto analogue and metabolite.

INTRODUCTION

Risperidone (**1**) known as typical second-generation antipsychotic drug substance, it belongs to benzisoxazole class of compounds. Risperidone is chemically known as 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-ethyl]-6,7,8,9-tetrahydro-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin -4-one. It is marketed by Janssen Pharmaceutica Inc., under the principal trade names **Risperdal®**, **Consta®** [1].

Risperidone (**1**) possesses extremely potent serotonin-5HT$_2$ and potent dopamine D$_2$ antagonistic properties [2]. Risperidone is available in oral solid dose (tablet), oral solution and intra muscular injections. Its maximum daily dose is 16 mg per day. This drug is used for the treatment of schizophrenia and related disorders. Schizophrenia is psychotic disorder characterized by extreme disturbances of cognition and thought affecting language, perception and sense of self [3] (approximately 1% of the world population). It is also useful to treat other psychotic disorders including acute bipolar mania [4].



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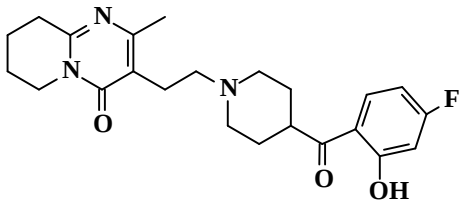


(2)

Chemical structures of Risperidone (1) & Risperidone impurity G (2)

Risperidone metabolic pathways are reported in literature [5, 6, 10]. The major metabolites of Risperidone are hydroxylation at 9 / 7 position of piperido-pyrimidine ring, these are 9-hydroxy Risperidone (currently known as Paliperidone drug substance) [6] and 7-hydroxy Risperidone, and cleavage of the benzisoxazole moiety to a carbonyl and phenol functions (Risperidone Hydroxy Keto analogue, **2,** currently known as Risperidone Impurity G) [9]. In this article we describe synthesis of Risperidone impurity G, chemically known as 3-[2-[4-(4-fluoro-2-hydroxybenzoyl)piperidin-1-yl]ethyl]-2-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**2**, Risperidone hydroxy keto analogue) and its structural confirmation by spectral analysis.

EXPERIMENTAL SECTION

In general, solvents & reagents were used as purchased without further purification. Melting points were determined by Polman melting point apparatus (Model No. mp-96) and are uncorrected. The IR spectra (ν max cm^{-1}) were recorded on Perkin-Elmer FT-IR spectrophotometer. The ^{1}H NMR, ^{13}C NMR spectra were recorded on 300 MHz, Bruker-Avance instrument using TMS as an internal standard. The mass spectra were scanned on Perkin-Elmer SCIEX API 2000 instrument. The compound **2** is reported as metabolite of Risperidone in literature [5, 6, 10], till date there is no reports of its synthesis and characterization. The synthesis of compound **2** by two different approaches is described in this section.

Preparation of 3-[2-[4-(4-fluoro-2-hydroxybenzoyl)piperidin-1-yl]ethyl]-2-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (2, Risperidone impurity G, through first approach)

3(2-Chloroethyl)-6,7,8,9-tetrahydro-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one hydrochloride **4** (5.00 g, 19.01 mmol) and (4-fluoro-2-hydroxyphenyl) (piperidin-4-yl)methanone hydrochloride **5** (5.51 g, 24.71 mmol) were added to methanol (70 mL). Triethylamine (9.37 g, 92.77 mmol) was added at 25-30 °C and raised the reaction mass temperature to reflux (60-63 °C) and continued the reflux for 3 h. Completion of reaction was monitored by HPLC. Reaction mixture was cooled to 10-15 °C. The product was isolated by filtration to yield compound **2** (crude, 4.97 g). Further, repeated crystallizations from methanol gave substantially pure compound **2** (3.9 g, 44.3 %). Melting Point: 302-306 °C; IR(KBr) Cm^{-1}: 1655.1 (C=O, str.), 1121.1 (Ar-F, str.);1H NMR in DMSO-d_6 : δ 1.76-1.80 (m, 2H, **CH_2**), 1.84-1.86 (m, 6H,3 x **CH_2**), 2.16 (m, 2H, **CH_2**), 2.38 (s, 3H, **CH_3**), 2.51 (m, 2H, **CH_2**), 2.56 (m, 2H, **CH_2**), 2.75 (t, 2H, **CH_2**, *J* = 9.0 Hz), 2.96-2.99 (m, 3H, **CH_2**, **CH**), 3.75-3.79 (t, 2H, **CH_2**, *J* = 9.0 Hz), 6.77-6.83 (m, 2H, **Ar-H**), 8.02 (t, 1H, **Ar-H**, *J* = 15.0 Hz), 12.80 (brs, **Ar-OH, D_2O** Exchangeable proton); ^{13}C NMR in DMSO-d_6 : δ 18.5, 20.9, 21.3, 23.3, 28.5, 30.7, 42.1, 43.7, 52.4, 56.3, 104.1, 104.4, 106.8, 107.1, 116.9, 133.4, 133.6, 156.1, 157.7, 161.6, 164.5, 167.8, 207.4; Mass analysis (m/z): 414.1 [$(M+H)^+$]; Anal. Calcd. for $C_{23}H_{28}N_3O_3F$ (413.49), C, 66.81; H, 6.83; N, 10.16%; found: C, 66.35; H, 6.75; N,10.02%.

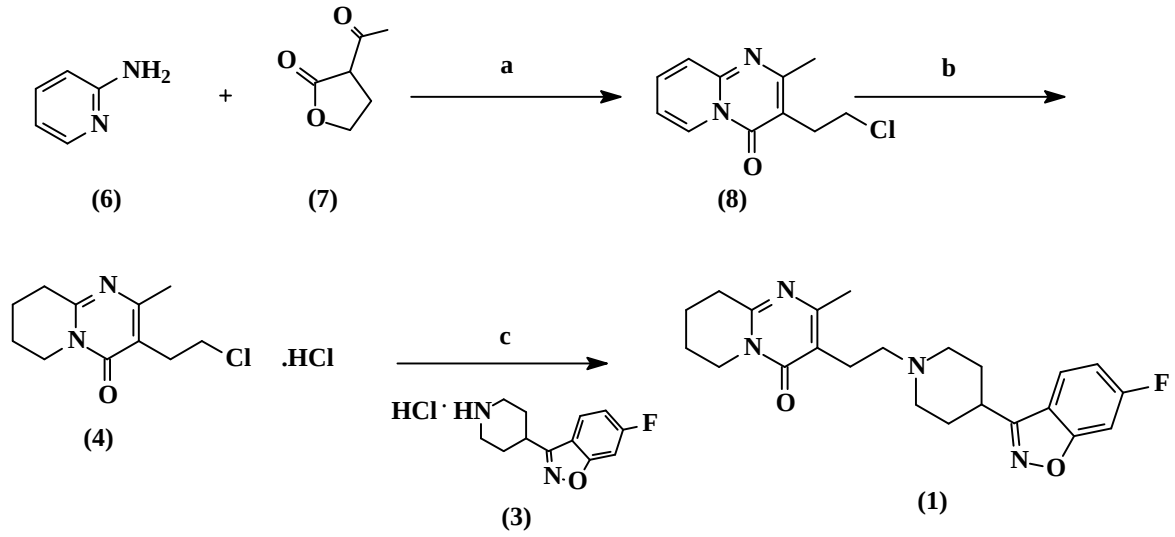
Preparation of 3-[2-[4-(4-fluoro-2-hydroxybenzoyl)piperidin-1-yl]ethyl]-2-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (2, Risperidone impurity G, through second approach)

3[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**1**, 5.00 g, 12.19 mmol) was suspended in methanol (200 mL) and heated to get a clear solution. Triethylamine (1.25 g, 12.37 mmol) and 10% palladium on charcoal (0.5 g, 50% wet, RD 9210) were added at 25-30 °C. The mixture subjected to the catalytic reduction by applied 3.3-3.5 kg/Cm^2 hydrogen pressure at 25-30 °C, continued for 10 hrs, Completion of reaction was monitored by HPLC. Reaction mixture was filtered over hyflo bed and pH of the filtrate was adjusted to 3.3 with 5% aqueous hydrochloric acid, distilled up to a volume of 30 mL and cooled to 10-15 °C. The separated product was isolated by filtration and washed with chilled methanol (2 X 5 mL, 2-8 °C) to yield compound **2** (4.00 g, 79.4%). Melting Point: 302-306 °C, Mixed melting Point with sample

prepared by first method not dispersed. The ^{1}H NMR, ^{13}C NMR, IR and Mass spectral data which are identical with the data for product synthesized from the first approach have been given in above experiment**.**

RESULT AND DISCUSSION

Several synthetic approaches are available for preparation of Risperidone (**1**) in literature; the most efficient method [11] describes the following procedure (**Scheme-1**). A key intermediate, 3-[2-chloroethyl]-6,7,8,9-tetrahydro-2-methyl-4*H*-pyrido[1,2-*a*]-pyrimidin-4-one (**4**), was synthesized by reacting 2-aminopyridine (**6**) with 3-acetyldihydrofuran-2(3*H*)-one (2-acetylbutyrolactone, **7**) through a bi-molecular cycloaddition reaction and further chlorinated with thionyl chloride to give 3-[2-chloroethyl-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one mono hydrochloride (**8**). Compound **8** was then hydrogenated to produce **4**, which is then coupled with 6-fluoro-3-(4-piperidinyl)[1,2]-benzisoxazole hydrochloride (**4**) using Sodium bicarbonate as base in methyl isobutyl ketone solvent to give the desired Risperidone (**1**) (**Scheme – 1**).



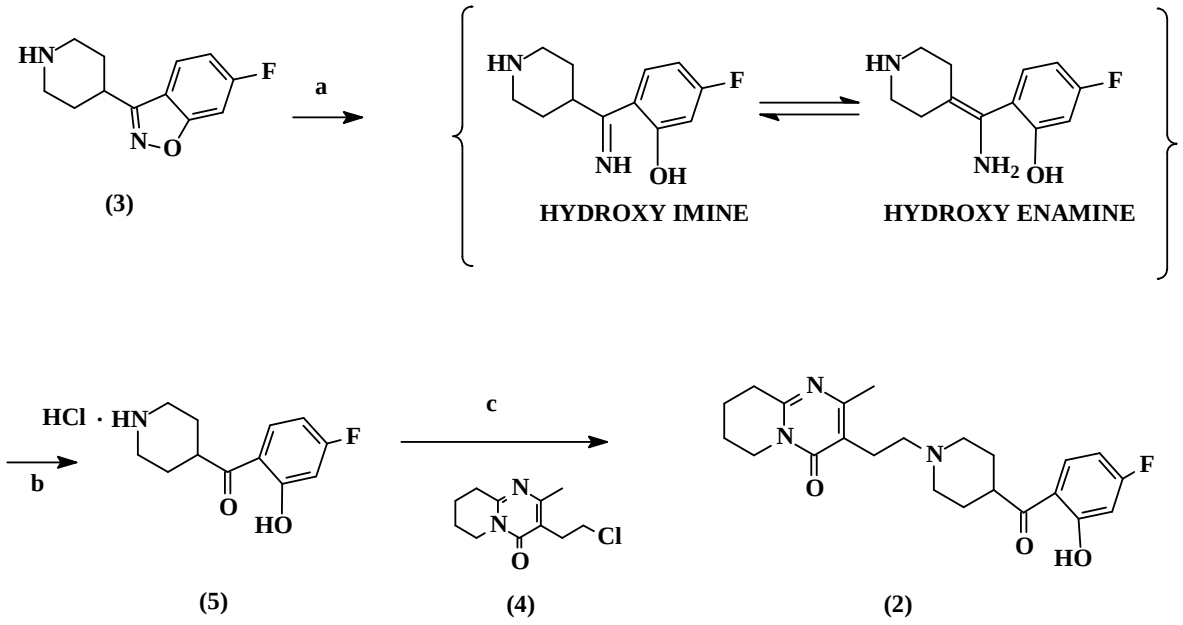
Scheme–1: Reagents and conditions: a) PTSA, $SOCl_2$; b) Pd/C; c) $NaHCO_3$, MIBK

Risperidone Hydroxy keto analogue (**2)** is known as one of the metabolites of Risperidone **1** and also reported as impurity G in European pharmacopoeia [9]. Impurities are having vital role in pharmaceutical industry in active pharmaceutical ingredient [7, 8]. This compound **2** was independently prepared from compound **5**. Further, compound **5** was condensed with **4** in presence of triethylamine as base in methanol as solvent to provide pure compound **2** (**Scheme–2**).

This impurity G was also prepared by second approach, compound **1** produces compound **2** by catalytic reductive cleavage in basic medium and compounds isolated at acidic pH (**Scheme–3**).

FIRST APPROACH:

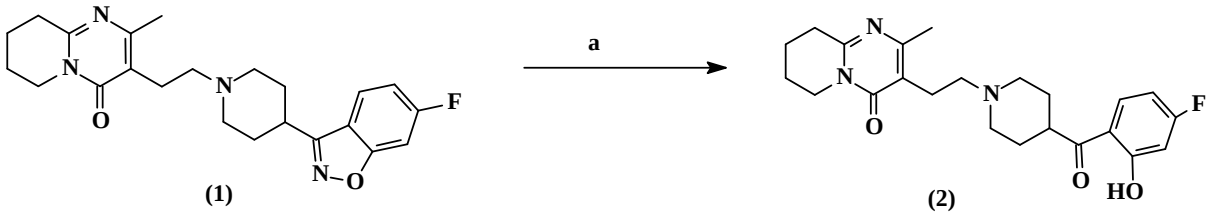
This approach involves reductive cleavage of isoxazole ring to produce a hydroxy imine / enamine intermediate that undergoes conversion to the hydroxy ketone (**5**) under acidic condition. Compound **5** was reacted with **4** to produce the compound **2**.



Scheme–2: Reagents and conditions: **a)** Methanol, TEA, 10% Pd/C, 12 h; **b**) 5% Aq. HCl;
c) Methanol, TEA, 12 h, ~ 44%

SECOND APPROACH:

In this approach reductive cleavage of isoxazole moiety in compound **1** produce the compound **2**.



Scheme–3: Reagents and conditions: a) Methanol, TEA, 10% Pd/C, 12 h; 5% Aq. HCl, ~ 80 %

Compound **5** is prepared from compound **3** through catalytic reductive cleavage of 3-substituted 1,2-benzisoxazole **3**. The mass spectrum of compound **2** showed a protonated molecular ion at *m/z* 414.1 amu [$(M+H)^+$], which suggests the molecular weight of compound **2** is 413. In comparison with Risperidone **1**, ^{1}H NMR spectrum showed *brs at* δ 12.43 ppm corresponding to one phenolic OH and exchangeable by D_2O analysis and in ^{13}C NMR showed additional characteristic carbonyl carbon signal of at δ 207.4 ppm were observed. This compound **2** was spiked with Risperidone sample containing compound **2** and confirmed the related substance. The ^{1}H NMR, ^{13}C NMR, IR and Mass spectral data are identical to the product (**2**) synthesized from first approach and second approach. This hydroxy keto impurities was formed up to ~ 0.15% by HPLC in final reactions, however during isolation of crude product ~ 0.08% and this impurity was found after final purification ~ 0.02%. This impurity **2** is process related impurity; this impurity also originates during Risperidone (**1**) synthesis from compound **3** and **4**. Compound **5** is present as an impurity in compound **3**. This can be controlled by raw material specifications / purification (compound **3**).

CONCLUSION

We described the preparation of Risperidone impurity G, which was characterized by it spectral data and confirmed as 3-[2-[4-(4-fluoro-2-hydroxybenzoyl)piperidin-1-yl]ethyl]2-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**2**), by ^{1}H NMR, ^{13}C NMR, IR and Mass spectral data. Synthesized compound by both approaches are identical by its spectral analysis. We obtained the higher reaction efficiency in second approach.

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