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Synthesis of related substances of antipsychotic drug Risperidone

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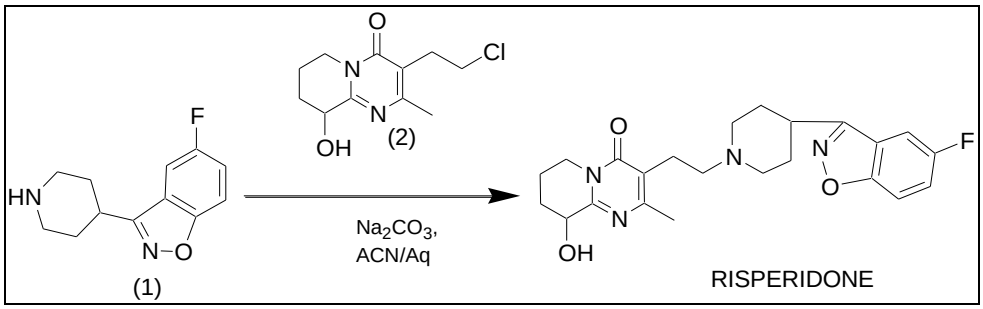
Abstract
Risperidone is a typical orally active antipsychotic agent for bipolar disorders. It belongs to the chemical class of benzisoxazole derivatives and chemically, it is 4-[2-[4-(6-fluorobenzo[*d*]isoxazol-3-yl)-1-piperidyl] ethyl]-3-methyl-2, 6 diazabicyclo [4.4.0] deca-1, 3-dien-5-one. European pharmacopeia related substances A, B, C, D, E and G and others (impurities) have been obtained during its synthesis. The present work describes the detection, origin, synthesis, characterization and control of the related substances, which may improve the commercial process.

Keywords: Risperidone, impurities, antipsychotic, synthesis

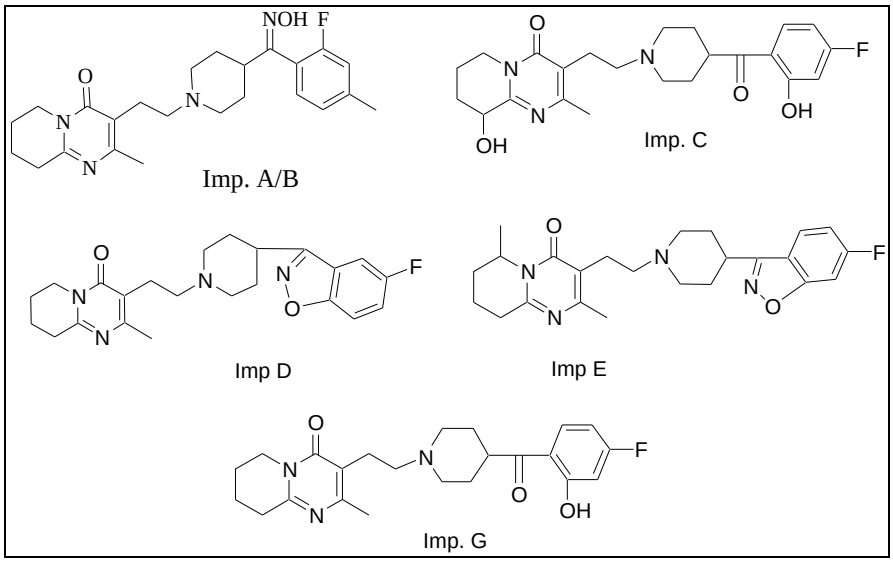
Introduction
Risperidone is a typical orally active antipsychotic agent for bipolar disorders. It belongs to the chemical class of benzisoxazole derivatives and chemically, it is 3-[2-[4-(6-fluorobenzo[*d*]isoxazol-3-yl)-1-piperidyl] ethyl]-2-methyl-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one. It is a dopamine antagonist possessing antiserotonergic, antiadrenergic and antihistaminergic properties [1, 2]. The drug was developed by Janssen-Cilag, subsidiary of Johnson & Johnson, and first released in 1994. It is a serotonin-Dopamine Antagonist. European pharmacopeia related substances A, B, C, D, E and G and others (impurities) have been reported during laboratory process and in plant process as well. The present work describes the detection, origin, synthesis, characterization and control of the related substances, thereby improving the commercial process. One of the impurity C, known as paliperidone [3], showed potent activity and is being used as a second generation antipsychotic drug.

Material and methods
Risperidone can be prepared [5] by refluxing the reaction of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole hydrochloride of the formula (1) with 3-(2-chloroethyl)-2-methyl, 6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one of formula (2) which are commercially available, in an environment friendly basic aqueous solution or suspension to obtain crude risperidone rapidly and efficiently.



The presence of impurities in an Active Pharmaceutical Ingredient (API) can impact on the quality and safety of the drug product. International Conference on Harmonization (ICH) guidelines recommends identifying and characterizing all impurities in API at a level of ≥ 0.10% [4]. More often the synthesis of impurities are not described in the literature which makes it even more difficult for the organic chemist who must then design a synthesis, which is time consuming.

The development of a drug substance is incomplete without the identification of an impurity profile involved in the process. Thus in our study we explored the formation, identification, synthesis and characterization of impurities found during synthesis of risperidone. This study will be of immense help for organic chemist to understand the potential impurities in risperidone synthesis and thereby to obtain pure compound. Structure of synthesized impurities is given as follows.

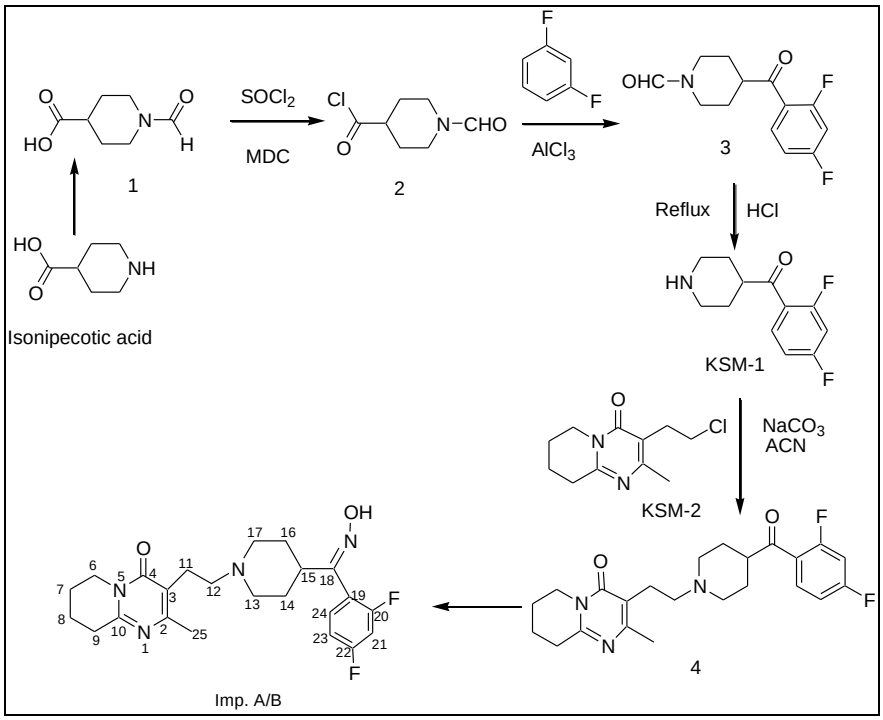


Since one of the reported impurities i.e. impurity C is already being used as a potential antipsychotic agent [1] and is known in the market by the name Paliperidone, the other impurities were objects of our interest from synthetic point of view. Impurity C was not synthesized as it is already known.

Results and Discussion

In this article work regarding the synthesis and characterization of the various potential impurities of Risperidone has been disclosed.

Preparation of Impurity A & B



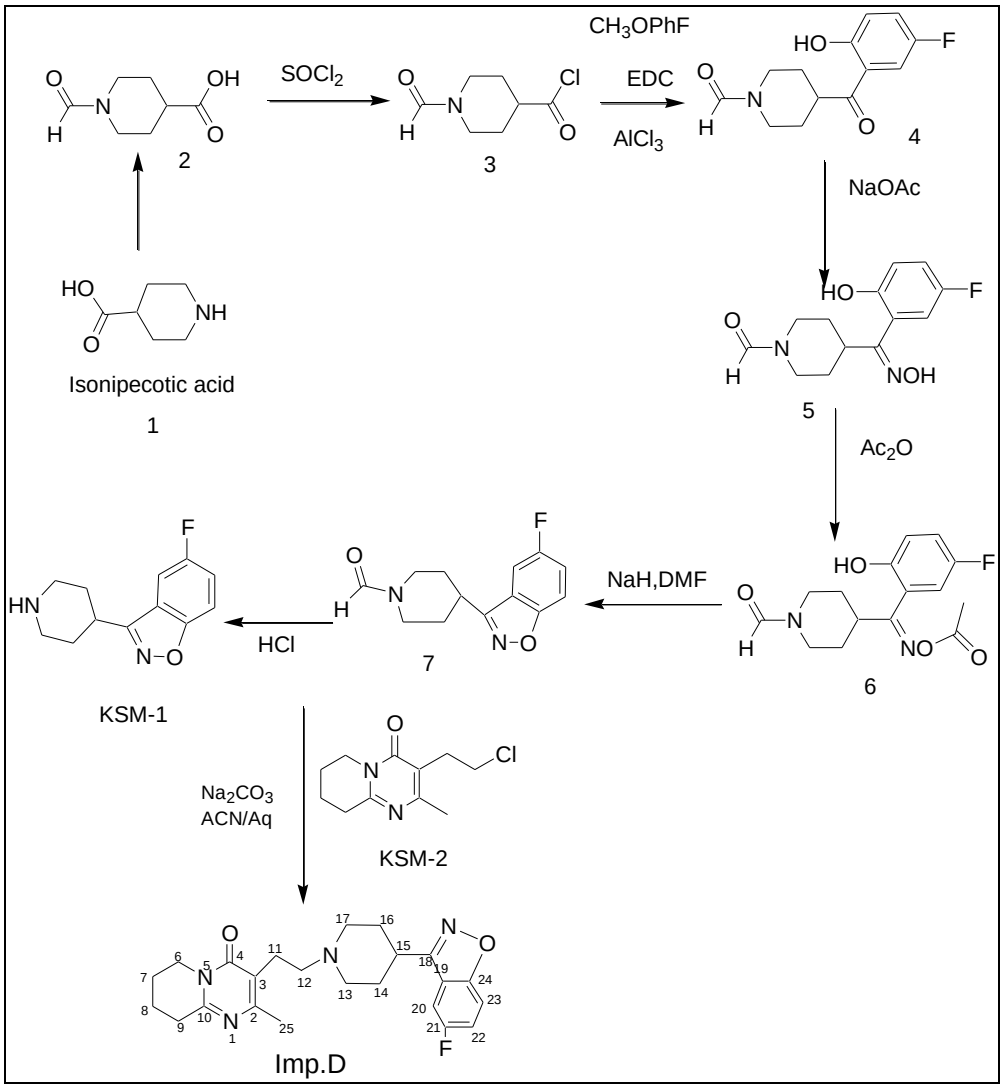
These isomeric impurities (mixture of A&B) are formed by oxime formation of a keto compound (4) which is formed by the condensation of 3-(2-chloroethyl)-2-methyl-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one (KSM-2 in fig.3) with 4-(2,3-difluorobenzoyl)piperdine(KSM-1in fig.3) in acetonitrile (ACN) using Na_2CO_3 as a base. 4-(2,3-difluorobenzoyl)piperdine is prepared as shown in the above scheme. N-formyl isonipecotic acid from isonipecotic acid was formed using formic acid in the presence of acetic anhydride at temperature 10-15 °C for 13-14 hours. After removal of acetic anhydride & formic acid under vacuum at 75 °C, Isopropyl alcohol was added into the residue. The reaction mixture was chilled upto 0-5 °C for 2 hours. White solid cake was formed. This cake was charged into the solution of thionyl chloride in dichloromethane. It was stirred at 40 °C for 2 hours. The solvent was removed under reduced

pressure to give yellowish oil. The oil was cooled up to 0-5°C & meta difluoro benzene in dichloromethane was added slowly in the presence aluminium chloride ($AlCl_3$). The reaction mixture was stirred at room temperature for overnight. The reaction mixture was quenched into the ice cool water and extracted with dichloromethane (MDC). The organic layer was washed, dried and concentrated to give viscous mass of 4-(2,3-difluorobenzoyl) piperdin-1-carbaldehyde (3), which on HCl treatment at reflux gave the 4-(2,3-difluorobenzoyl) piperdine as an oil. The 4-(2,3-difluorobenzoyl) piperdine and sodium carbonate in acetonitrile was heated to 60°C and 3-(2-chloroethyl)-2-methyl-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one in water was added. The reaction mixture was stirred at 60 °C for 13 hours. The reaction mixture was cooled and extracted with MDC. The organic layer was removed to give syrupy liquid (4). Impurity A&B was obtained as isomeric mixture by oximation of the keto compound (4) with Hydroxyl amine hydrochloride. The ketone (4) (syrupy liquid) was dissolved in methanol and charged with hydroxyl ammonium hydrochloride (HAH) at 25-30° C, added sodium acetate and stirred for 24 hours and then washed with MDC. Aqueous layer was basified with sodium carbonate (pH 8) and extracted the product in MDC. The MDC layer was washed with water, dried over anhydrous sodium sulphate and then it was distilled of completely. It was crystallized using diisopropyl ether, filtered and dried the product Impurity A/B

Preparation of Impurity C

Since the impurity C is well known named palperidone as antipsychotic drug[6]. Since many syntheses are reported in literature. It was not investigated further.

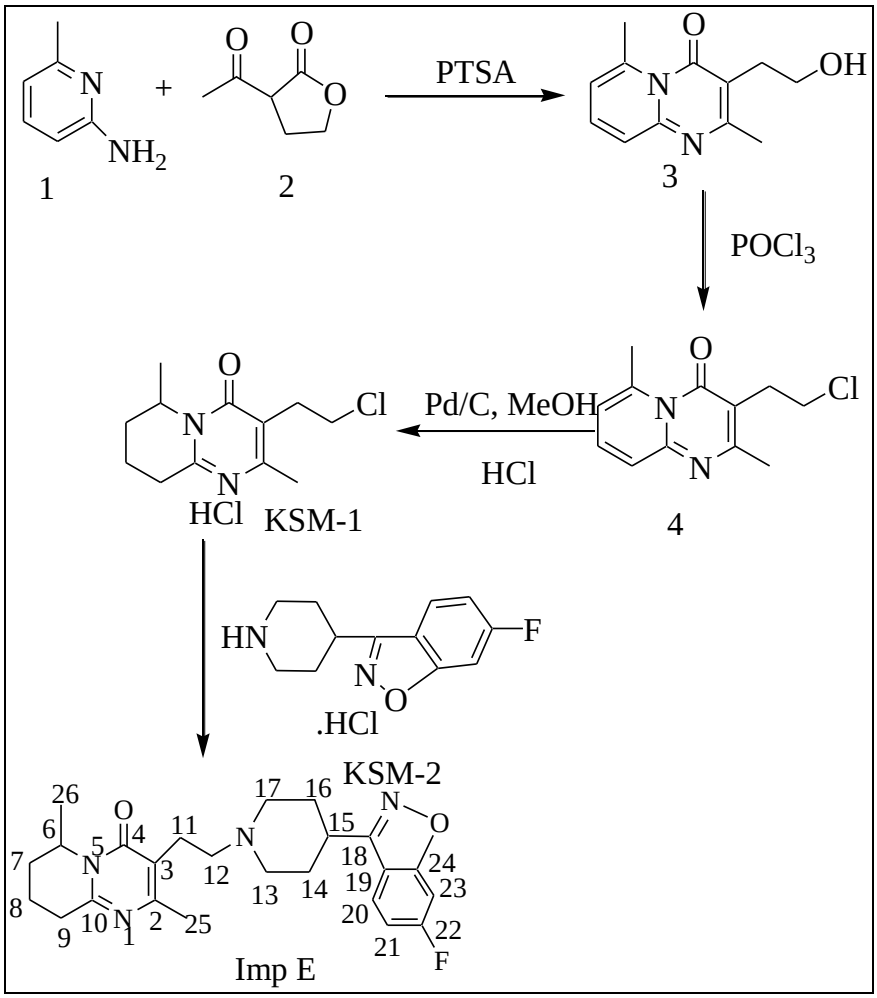
Preparation of Impurity D



The impurity D was formed by the condensation of 6-fluoro-3-(4-piperidyl)-1,2-benzoisoxazole Hydrochloride (KSM-1 in Fig.4) with 3-(2-chloroethyl)-2-methyl-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one in ACN using Na_2CO_3 as base. N-formyl isonipecotic acid from isonipecotic acid was formed using formic acid in the presence of acetic anhydride at temperature 10-15 °C for 13-14 hours. After removal of acetic anhydride & formic acid under vacuum at 75 °C, isopropyl alcohol was added into the residue. The reaction mixture was chilled upto 0-5 °C for 2 hours. White solid cake was formed. This cake was charged into the solution of thionyl chloride in dichloromethane. It was stirred at 40°C for 2 hours. The solvent was removed under reduced pressure to give yellowish oil. The oil was cooled upto 0-5 °C & p-fluoro anisole in dichloroethane was added slowly in the presence of $AlCl_3$. The reaction mixture was stirred at room temperature for overnight. The reaction mixture was quenched into the ice cool water and extracted with MDC. The organic layer was washed, dried and concentrated to give viscous mass. To the solution of (4) in ethanol was added the solution of hydroxyl

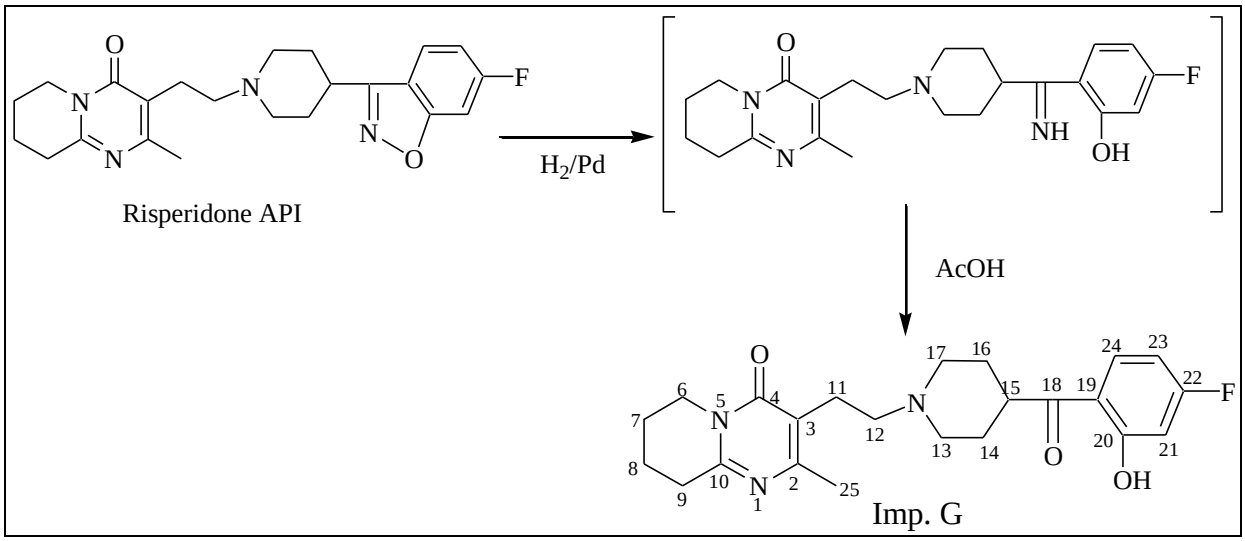
amine sulphate and sodium acetate in DM water. The reaction mixture was stirred at reflux condition for 20 hours. After removal of ethanol, DM water & MDC was added. The solution was transferred to a separating funnel. The organic layer was dried and concentrated to give oily mass of oxime (5). To the solution of (5) in MDC was added acetic anhydride and stirred the reaction mass at room temperature for 16-18 hours to give acetyl product (6). The compound (6) in dimethylformamide (DMF) was added in the solution of sodium hydride & DMF under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 60 hours. DM water was added and extracted with MDC. The solvent was removed under reduced pressure to give brown colour solution. HCl was added to this brownish solution and stirred at 80-85°C for 6 hours to give solid material 6-fluoro-3-(4-piperidyl)-1,2-benzoisoxazole Hydrochloride. This key material 6-fluoro-3-(4-piperidyl)-1,2-benzoisoxazole Hydrochloride and sodium carbonate in acetonitrile was heated to 60°C and another key material 3-(2-chloroethyl)-2-methyl-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one in water was added. The reaction mixture was stirred at 60 °C for 16 hours. The reaction mixture was cooled and extracted with MDC. The organic layer was removed and the residue was crystalized by diisopropyl ether and acetonitrile to give impurity D.

Preparation of Impurity E



The impurity E is formed by the condensation of 3-(2-chloroethyl)-2,6-dimethyl-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one Hydrochloride (KSM-1 in Fig.5) with 3-(2-chloroethyl)-2-methyl-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one in ACN using Na_2CO_3 as base. The key material 3-(2-chloroethyl)-2,6-dimethyl-6,7,8,9-tetrahydro-4H-pyrido [1,2-a]pyrimidin-4-one Hydrochloride is synthesized as shown in the above scheme. To the solution of 2-acetyl butyrolactone & 6-methylpyridin-2-amine in toluene was added para toluene sulfonic acid. The reaction mixture was stirred at reflux temperature for 48 hours. Toluene was completely removed under reduced pressure to give slurry mass (3). The compound (3) was crystallised by toluene-cyclohexane mixture (1:1). To the solution of (3) in toluene was added $POCl_3$ at temperature 75 °C. Stirred the reaction mixture for 2 hours at 90 °C. The reaction mixture was quenched into ice water and adjusting the pH 9.0 using of liq. Ammonia. The reaction mixture was extracted with MDC. The organic layer was dried concentrated under vacuum. Isopropyl alcohol (IPA) was added & stirred at 55 °C for 30 minutes. It was crystallized on chilling to give compound (4). The compound (4) in methanol was hydrogenated at room temperature and 5-6 kg/cm^2 pressure in autoclave in presence of 10% palladium on charcoal for 3 hours. Filtered the reaction mass and HCl was added. IPA was used for crystallization to 3-(2-chloroethyl)-2,6-dimethyl-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one Hydrochloride. The condensation reaction of this key starting material with 3-(2-chloroethyl)-2-methyl-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one was carried out as same for others.

Preparation of Impurity G



An ethanolic solution of Risperidone was hydrogenated at RT at atmospheric pressure using 10% palladium on charcoal. When hydrogen had been consumed after 5-6 Hours, the reaction mass was filtered evaporated to get a yellow oil. Dilute acetic acid was added to this oil and stirred the reaction mixture overnight at RT. Then it was diluted with water and extracted with ether which was washed with sodium bicarbonate solution, concentrated and dried. It was further purified by column chromatography using 10%MeOH/ MDC.

Conclusions

This work on synthesis of different impurities of Risperidone is a prerequisite for better understanding the route of formation pathway in Risperidone. Keeping in view the regulatory importance of Risperidone impurities, our efforts to synthesize and characterize them effectively prove to be valuable.

Experimental

Materials and instruments

All solvents and reagents were purchased from the suppliers and used without purification. The NMR spectra of the compound were recorded on 400 MHz Bruker's NMR spectrometer (av400). The chemical shifts were recorded in parts per million (δppm) relative to TMS. FT-IR (Perkin Elmer) spectrometer was used to record the IR spectrum of the compound. KBr pellet of the compound was prepared by the standard method and the spectrum was recorded at 4 cm^{-1} resolution from 400 cm^{-1} – 4000 cm^{-1}. Mass spectra of the compound were recorded on Q-Tof LC-MS (Waters).

3-(2-{4-[(2,4-Difluoro-phenyl)-hydroxyimino-methyl]-piperidin-1-yl}-ethyl)-2-methyl-6,7,8,9-tetrahydro-pyrido[1,2-a]pyrimidin-4-one (Impurity A and B)

These isomeric impurities (mixture of A&B) are formed by oxime formation of a keto compound (4) which is formed by the condensation of 3-(2-chloroethyl)-2-methyl-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one (KSM-2) with 4-(2,3-difluorobenzoyl)piperdine (KSM-1) in ACN using Na_2CO_3 as a base. KSM-1 was synthesized from isonipecotic acid as an oil. Impurity A/B was obtained as white solid., m/z 431.14[M+1], IR(KBr): 3430.36(O-H str.), 2804.3C-H str. Aliphatic), 2947.97(C-H str. aromatic), 1648.51(C=O str.), 1536.83(C=C str.), 1140.17(C-F str.), ^{1}H NMR (MHz); δ 1.642-1.955(m, 10H, H-7,8,11, 14, 16), 2.62(s, 3H, H-25), 2.482-2.492(m, 2H, H-9), 2.739-2.781(m, 2H, H-12), 2.831-2.863(m, 2H, H-17), 3.107-3.119(m,2H, H-13), 3.308-3.316(m,1H, H-15), 3.889-3.920(t,4.5Hz, 2H. H-6), 6.805-6.883 (m, 2H, H-23, 24), 7.153-7.210(m, 1H, H-21), 8.606(brs, 1H, OH).

3-{2-[4-(5-Fluoro-benzo[d]isoxazol-3-yl)-piperidin-1-yl]-ethyl}-2-methyl-6,7,8,9-tetrahydro-pyrido[1,2-a]pyrimidin-4-one (Impurity D)

The impurity D is formed by the condensation of 4-(5-fluoro-1,2-benzoxazol-3-yl)piperidine-1(KSM-1) with 3-(chloroethyl 6,7,8,9 tetrahydro)-2-methyl-4H-pyrido[1,2,a]pyrimidine-4-one (KSM-2) in ACN using Na_2CO_3 as base. KSM-1 is synthesized as shown in the above scheme. It is started by formylation of isonipecotic acid followed by thionyl chloride reaction followed by Friedel Craft reaction followed by oximation then acetylation and oxazolone ring formation in basic condition. Impurity D is obtained as a light yellow solid. m/z411 [M+1], IR (KBr): 2947.20(C-H str.aliphatic), 3040.99(C-H str. aromatic), 1645.73(C=Ostr.) 1531.77(C=Cstr.), 1185.12(C-F str.); 1H NMR (400 MHz) δ1.242-1.399(m, 2H, H-8), 1.859-2.304(m, 8H, H-7,11,14,16), 2.328(s, 3H, H-25), 2.730-2.928 (m, 6H, H-9,12,17)., 3.262(brs, 1H, H-15), 3.328-3.400(m, 2H, H-13), 3.840-3.910(m, 2H, H-6), 7.272-7.316(m, 1H, H-23), 7.430-7.454(d, 1H, H-20), 7.500-7.532(m,1H, H-22).

3-[2-[4-(6-fluorobenzo[*d*]isoxazol-3-yl)-1-piperidyl] ethyl] -2,6-dimethyl-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one. (Impurity E)

The impurity E is formed by the condensation of 3-(2-chloroethyl)-2,6 dimethyl- 6,7,8,9 tetrahydro-4H-pyrido[1,2,a]pyrimidine-4-one with 6-fluoro-3-(piperidin-4-yl)benzo[d]isoxazole in ACN using Na_2CO_3 as base. The first key starting material is synthesized by condensation of 2-acetyl butyrolactone with 6-methylpyridin-2-amine as shown in the above scheme. The impurity E was obtained as a white solid, m/z 425 [M+1], IR(KBr): 2940.32 (C-H str. Aliphatic), 3038.79 (C-H str. aromatic), 1646.77(C=O str.), 1643.26 (C=O), 1533.87(C=C str.), 1186.24(C-F str.),^{1}H NMR (400MHz); δ1.325-1.340(d, 3H, H-26),1.847-2.211 (m, 8H, H-7, 8, 14, 16), 2.306-2.338(m, 2H, H-11), 2.431(s, 3H, H-25), 2.603-2.643(m, 2H, H-9), 2.837-2.941(m, 2H, H-17),

2.960-2.982(m,2H, H-13), 3.148-3.188 (m, 1H, H-15), 3.251-3.280(m, 2H, H-12), 4.061-4.089(m, 1H, H-6), 7.126-7.168(m, 1H, H-21), 7.32l2-7.356 (dd, 1H, H-23), 7.789-7.814(dd, 1H, 20).

3-{2-[4-(4-Fluoro-2-hydroxy-benzoyl)-piperidin-1-yl]-ethyl}-2-methyl-6,7,8,9-tetrahydro-pyrido[1,2-a]pyrimidin-4-one (Impurity G)

Impurity G was synthesized by hydrogenation then followed by acid hydrolysis of directly risperidone API. Impurity G was obtained as a light brown solid, m/z 414 [M+1], IR(KBr): 3413.85(O-H str.), 2953.396C-H str. Aliphatic), C-H str. aromatic), 1726.851(C=O str.), 1643.26 (C=O), 1532.83(C=C str.), 1127.09(C-F str.),^{1}H NMR (400MHz,); δ 1.9423-2.038(m, 10H, H-7,8,11, 14, 16), 2.291(s, 3H, H-25), 2.606-2.631(m, 2H, H-9), 2.742-2.764(m, 2H, H-12), 2.819-2.888(m, 2H, H-13, 17), 3.321-3.350(m,1H, H-15), 3.388-3.918 (t,4.5Hz, 2H. H-6), 4.357(brs, OH), 6.599-6.682(m, 2H, H-23, 24), 7.718-7.755 (t, 1H, H-21).

Acknowledgements

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