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Research Article

SYNTHESIS, ISOLATION AND CHARACTERIZATION OF RELATED SUBSTANCES, DEGRADATION AND POTENTIAL IMPURITIES OF ILOPERIDONE

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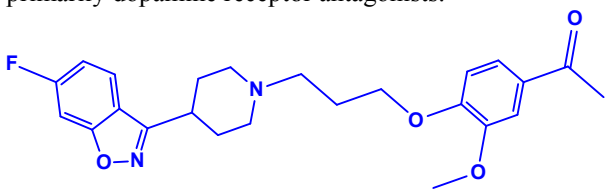
ABSTRACT

Five close related substances (unknown impurities), four processes related (known impurities) substances were identified during the development of laboratory process and pilot scale preparation of an antipsychotic drug Iloperidone. Namely; Iloperidone related compound-1(I), Iloperidone related compound-2 (II), Iloperidone chalcone related dimer impurity (degraded) (III), Dehydro Iloperidone analogue (reductive impurity) (IV), Iloperidone process related compound-3 (hydrolyze impurity) (V), Iloperidone process related dimer impurity-14 (VI), Iloperidone process related dimer impurity-9 (VII), Iloperidone N-oxide impurity-11 (VIII), Iloperidone process related Desflouroanalogue of Iloperidone impurity-8 (IX). To the best of our knowledge, impurities I, II, III, IV and IX are not yet reported in the literature. An alternative synthetic protocol for Iloperidone and its impurities were designed and reported for the first time. All the synthesized compounds were characterized by using FTIR, MASS and NMR spectrometry. The detection, origin, synthesis, characterization and control of these potential related substances, thereby providing a commercial method to synthesize substantially pure Iloperidone was described in detail.

INTRODUCTION

Second generation atypical antipsychotic drug, Iloperidone belongs to benzisoxazole class of compounds. It is chemically designated as 1-(4-{3-[4-(6-fluoro-benzo[d]isoxazol-3-yl)-piperidin-1-yl]-propoxy}-3-methoxy-phenyl)-ethanone **1**(**figure 1**). Initially, Aventis pharma (originator) and Tatan pharma (licensee) are marketed under the trade name of Fanapt, Fanapta and Zomaril (previously known as). Later, it was co-developed by Novartis and Vanda, then marketed as Resolor® by Novartis in U.S, approved by the U.S. Food and Drug administration (FDA) for the treatment of acute schizophrenia in adults in the United States. Iloperidone is a centrally active dopaminergic (D_{2A} and D_3), and serotonergic ($5HT_{1A}$ and $5HT_6$) receptor antagonist[1] was found to block the sites of noradrenalin (α_{2C}) with a lower risk of extra pyramidal side effects and higher efficacy than first generation antipsychotic agents[2] which demonstrated in both in-Vitro and in-Vivo animal and human model of studies. It is also active as an antagonist at a low risk of anticholinergic adverse effects, minimal muscarinic and histaminic receptors. In addition, a pharmacogenomics study revealed that single nucleotide polymorphisms associated with an enhanced response to Iloperidone during acute treatment of schizophrenia. It is considered as an "atypical" antipsychotic because it displays serotonin receptor antagonism, similar to other atypical antipsychotics because of its safety and efficacy advantage over typical antipsychotics[3]. The older typical antipsychotics are primarily dopamine receptor antagonists.[4]



1

Figure 1 Chemical structure of Iloperidone

Drugs have become an important part of human life to combat with various deceases. At present time, most of the drugs are synthetically pure and these synthetic drugs certainly associate with various impurities either chemical or microbial. Many of these impurities are due to unwanted chemicals that remain with the active pharmaceutical ingredients (APIs), or developed during formulation, or upon aging of both API and formulation of medicines. Presence of close related products and process related impurities in the final bulk drug or active pharmaceutical Ingredient (API) may create stability related

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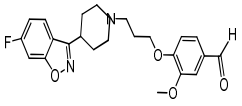
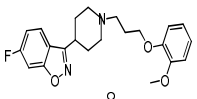
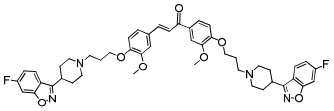
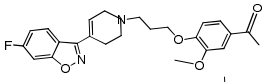
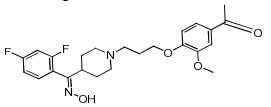
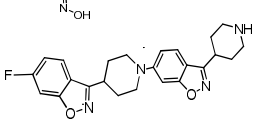
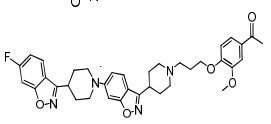
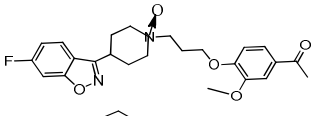
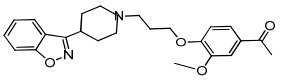
issues during formulations and activity related problems in the clinical trials due to their xenotoxic nature. They can impact on the quality and safety and efficacy of the drug substance. According to the International Conference on Harmonization (ICH) guidelines,[5] the acceptable amounts for known and unknown compounds in a final drug candidate of API must be less than 0.15 and 0.10% respectively. In order to meet this stringent regulatory requirement, the impurities associated with the drug should be identified and characterized thoroughly which referred as impurity profiling of drug substances (API). The impurity profiling involves identification and assessment of the quantity of an impurity in a pharmaceutical API. This study of APIs deals with the impurities are required in highly pure form to check the analytical data characteristics such as specificity, linearity, range, accuracy, precision, limit of detection (LOD), robustness limit of quantification (LQD), reproducibility, system suitability testing and relative retention factor.[6] The standard pharmacopoeias, such as the British Pharmacopoeia (BP) and the United States Pharmacopoeia (USP), are gradually incorporating limits to allowable levels of impurities presenting in the APIs of formulations. To have a thorough understanding of origin of impurity formation for antipsychotic agent Iloperidone, it is essential to have detailed information about various potential impurities and their mechanism of formation. In view of the importance of Iloperidone; we aimed to develop a laboratory process and pilot scale preparation of this drug and its various process related substances, degradation substances and enantiomeric impurities.[7-9]

Based on LC-MS studies and its fragmentation patterns, structures are assigned tentatively, synthesized and confirmed by spiking studies by HPLC.

Forced degradation study of iloperidone was reported under hydrolysis conditions (neutral, acidic and alkaline), oxidation, photolytic and thermal conditions to demonstrate the stability-indicating capability of the developed UPLC method suggested in the ICH Q_{2A} (R1).[10-12] The drug showed significant degradation under all the above conditions. On the whole, four novel degradation products were found under diverse conditions along with process related impurities which were not reported earlier.

In the present work, we are identified nine known and unknown related substance (metabolites and degradation products) impurities during the laboratory process development and pilot scale preparation of Iloperidone shown in Table 1. Their origin, novel synthesis, characterization and control of these related substances **I** to **IX** are described. Among these impurities, synthesis of four unknown impurities is not reported in the literature. Herein, we wish to report the identification, synthesis, and characterization of these new impurities of Iloperidone **1**. The HPLC analysis of Iloperidone confirms the nine impurity peaks along with the Iloperidone peak in the range of 0.05-0.15%.

Table 1 Impurity name, Synonyms used and source of Iloperidone and its impurities and molecular weights

Impurity name	Synonyms	Structure	Source	Mol. Wt.
Imp-I	Related compound 1		Process	412.21
Imp-II	Related compound 2		Process	384.44
Imp-III	chalcone related dimer impurity 2		Degraded	820.41
Imp-IV	Dehydro Iloperidone analogue		Process	424.21
Imp-V	Related compound 3		Process &Degraded	446.21
Imp-VI	Related dimer impurity 14		Process	420.1
Imp-VII	Related dimer impurity 9		Process	626.21
Imp-VIII	Related N-oxide impurity 11		Degraded	442.47
Imp-IX	Desflouro analogue of impurity 8		Process	408.49

Following are the related substances identified in Iloperidone 1

Synthetic process: 4-{3-[4-(6-fluoro-benzo[d]isoxazol-3-yl)-piperidin-1-yl]-propoxy}-3-methoxy-benzaldehyde(**I**), 6-fluoro-3-{1-[3-(2-methoxy-phenoxy)-propyl]-piperidin-4-yl}-benzo[d] isoxazole(**II**), 1,3-bis-(4-{3-[4-(6-fluoro-benzo[d]isoxazol-3-yl)-piperidin-1-yl]-propoxy}-3-methoxy-phenyl)-propenone(**III**), 1--(4-{3-[4-(6-fluoro-benzo[d]isoxazol-3-yl)-3,6-dihydro-2H-pyridin-1-yl]-propoxy}-3-methoxy-phenyl)-ethanone(**IV**), 1-[4-(3-{4-[(2,4-difluoro-phenyl)-hydroxyimino-methyl]-piperidin-1-yl}-propoxy)-phenyl]-ethanone(**V**),[3-(6-fluoro-benzo[d]isoxazol-3-yl)-propyl]-(3-piperidin-4-yl-benzo[d]isoxazol-6-yl)-amine (**VI**), 1-{4-[3-(4-{6-[-[4-(6-fluoro-benzo[d]isoxazol-3-yl)-piperidin-1-yl]-benzo[d]isoxazol-3-yl}-piperidin-1-yl)-propoxy]-3-methoxy-}-ethanone (**VII**), 1-(4-{3-[4-(6-Fluoro-benzo[d]isoxazol-3-yl)-piperidin-1-yl]-propoxy}-3-methoxy-phenyl)-ethanone N-oxide(**VIII**), 1-{4-[3-(4 benzo[d]isoxazol-3-yl-piperidin-1-yl)-propoxy]-3-methoxy-phenyl}-ethanone (**IX**).

A straight forward and common approach was reported for Iloperidone earlier.[13]The synthetic procedure involves the formation 6-fluoro-3-(1-formylpiperidin-4-yl)-1,2-benzisoxazole in 15.4% yield using hazardous reagent NaH in hot THF/DMF. Synthetic route demonstrated in the above process may be the best approach to accomplish the initial requirement of discovery studies. However, the development of a commercial process of new or known methodologies should ensure the industrial safety, cost efficiency and outmost purity is always a worthy contribution in the field of synthetic organic process research and development. The importance of these parameters, we aimed to develop a cost-efficient industrial process and demonstrated a novel synthetic route successfully with 95% yield and more than 99% chromatographic purity of the iloperidone product.

Thus, we have described an efficient, industrial scale novel synthetic protocol for synthesis of iloperidone **1**. During the synthesis of **1**, we have identified process related impurities, degradation products of iloperidone drug substance. To comprehend the complete impurity profile of **1** and to compare the extent of contamination of the impurities in **1**, synthesis of possible impurities was demonstrated.

Experimental Section

MATERIAL AND METHODS

Infrared spectra of compounds were recorded in KBr disc and in solid state using Perkin-Elmer model 1600 FTIR spectrophotometer (Perkin-Elmer, Norwalk, CT, USA). Electrospray ionization mass spectra were recorded on API 4000 triple quadruple instrument (MDSSCIEX, Concord, Ontario, Canada). LC-mass spectra were recorded on Agilent1100 series LC-MSD-TRAP-SL system mass spectrometer. Elemental analyses were performed on Hosli CH-Analyser and the results were within +0.35% of the calculated values. ^{1}H-NMR spectra was obtained in Deuterated solvents on a Bruker proton NMR spectrometer (Fallanden, Switzerland) at 400 MHz using Tetramethylsilane (TMS) as an internal standard. Chemical shift values and coupling constants are expressed in parts per million and Hz respectively. Melting points were determined by Polman melting point apparatus (Model No: MP-96) and are uncorrected. Column chromatography was performed using 100–200 mesh silica gel under nitrogen pressure (Flash chromatography) conditions. All the reagents and chemicals used were of 'reagent grade'.

Synthesis of Toluene-4-sulfonic acid 3-chloro-propyl ester 4

A solution of 3-chloropropan-1-ol **2** (12.8 g, 135.39mmol) in 75 mL dichloromethane and triethylamine (32.81g, 324.94mmol) were cooled (below -2 to10^{0}C) over a period of 10 minutes. Then added a solution of 4-methyl-benzenesulfonylchloride **3** (28.39g, 148.93mmol) in dichloromethane (50 mL) slowly over a period of 40 minutes and maintaining the reaction mass temperature at 10-15^{0}C under nitrogen atmosphere. The reaction mixture was further stirred for 3 hour at the same temperature. The progress of the reaction was monitored by thin layer chromatography (TLC). After completion of the reaction, the reaction mixture was quenched into 300 mL cold water. The reaction mass was acidified with conc. HCl and extracted the product with dichloromethane (2x200 mL). The combined organic layer was washed with brine solution (2x75mL), water (2x100 mL), dried over anhydrous sodium sulphate and concentrated under reduced pressure to obtain toluene-4-sulfonic acid 3-chloro-propyl ester **4** as an oily (32.01 g) product. The product was used without purification for the next step.

Synthesis of 1-[4-(3-chloro-propoxy)-3-methoxy-phenyl]-ethanone 6

To a stirred solution of 1-(4-hydroxy-3-methoxyphenyl) ethanone **5** (10 g, 60mmol), acetonitrile (40mL) and potassium carbonate (19.93 g, 144.43mmol) were charged at room temperature. Toluene-4-sulfonic acid 3-chloro-propyl ester **4** (16.46 g, 66.19mmol) in acetonitrile (40mL) was added drop wise at ambient temperature for 15 min and maintained at 65-70^{0}C for 3h. The reaction progress was monitored by TLC (methylene dichloride: methanol, 4:1); reaction contents were cooled to room temperature and filtered. Then, solvent was removed under reduced pressure below 60 ^{0}C and recrystallized from n-hexane (30 mL) as a low-melting white crystalline solid **6**. The dimer impurity **10** reported by Strupczewski et.al.[13]was well controlled (below 0.4%) during the synthesis of compound **6** without high-vacuum distillation. (13.50 g obtained yield: 92.71 %) (99.2% purity by HPLC), m.p. 61-63^{0}C; **FT-IR**: (KBr,v, cm^{-1}): 3071, 2963, 2932, 2841, 2878, 1669, 1596, 1587, 1521, 1465, 1451, 1419, 1354, 1276,1224, 1182, 1142, 1076, 1034, 873, 806, 756, 721; **^{1}H NMR**: (400 MHz, $CDCl_3$): δ 2.30-2.33 (m, 2H, C-CH_2-C), 2.56 (s, 3H, $COCH_3$), 3.76-3.79 (t, 2H, J = 6.4 Hz , Cl-CH_2-C), 3.91 (s, 3H, Ar-OCH_3), 4.22-4.25 (t, 2H, J = 6.2 Hz, C-CH_2-OAr), 6.90-6.92 (d,1H, J = 8.0 Hz), 7.52-7.57 (m,1H), 7.52-7.57 (m, 1H); **^{13}C NMR** ($CDCl_3$): 25.82, 31.71, 41.08, 55.60, 65.11, 110.26, 111.23, 122.80, 130.36, 148.98, 152.20, 196.25; **MS** (ESI, m/z): 243 [M + H]+, 265 [M + Na]+. **Anal.Calcd**. (%) for $C_{12}H_{15}ClO_3$ (242.70): C, 59.39; H, 6.23; **Found** (%): C, 59.28; H, 6.17

Synthesis of 1-(4-{3-[4-(6-Fluoro-benzo[d]isoxazol-3-yl)-piperidin-1-yl]-propoxy}-3-methoxy-phenyl)-ethanone 1

1-[4-(3-chloro-propoxy)-3-methoxy-phenyl]-ethanone **6** (8.0 g, 32.96mmol) and 6-fluoro-3-piperidin-4-yl-benzo[d]isoxazole hydrochloride **7** (7.61g, 29.66mmol) were added to methanol (70mL) and 8.0 mL of water at 25-30^{0}C. Diisopropyl ethyl amine (17.04 g, 131.65mmol) was added to above suspension at ambient temperature. The temperature of the reaction mass

increased slowly up to 65-70^{0}C and maintained at the same temperature for 16h. The reaction progress was monitored by TLC (chloroform: methanol, 4:1). The solvent was removed under reduced pressure below 65^{0}C and recrystallized from isopropyl alcohol (30 mL) under reflux and cool to below 0-2^{0}C obtained as a white crystalline wet solid. Obtained wet product was dried under vacuum at 50-55^{0}C for 1-2 h. Dry weight of **1** was 13.4g (95.37% yields based on **6**). Purity by HPLC: 99.45%. **FT-IR** (KBr, ν, cm^{-1}): 3031, 2949, 2779, 2746, 2822, 1669, 1614, 1585, 1510, 1462, 1448, 1415, 1380, 1313, 1262, 1221, 1177, 1150, 1123, 1077, 1034, 997, 985, 955,884, 876, 853, 812, 781, 643, 610, 569, 475; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.04−2.11(m, 6H), 2.13−2.18 (m, 2H, C-CH_2-C), 2.56−2.57 (s, 3H, $COCH_3$), 2.59−2.61 (t, 2H, N-CH_2-C), 3.03−3.10 (m, 3H), 3.92 (s, 3H, Ar-OCH_3), 4.11−4.20 (t, 2H, C-CH_2-OAr), 6.92−6.94 (d, 1H), 7.02−7.07 (dd, 1H), 7.22−7.25 (dd, 1H), 7.52−7.53 (d, 1H), 7.54−7.57 (dd, 1H), 7.70−7.77 (dd, 1H); **^{13}C NMR** ($CDCl_3$): 26.02, 26.40, 30.36, 34.34, 53.36, 54.90, 55.80, 67.16, 97.04, 97.31, 110.20, 111.02, 111.98,112.23, 117.12, 122.36, 122.46, 123.06, 130.11, 149.00, 152.66,160.91, 162.60, 163.53, 163.66, 165.09, 198.59.; **MS** (ESI, m/z): 427.2 [M + H]+. **Anal.Calcd** (%) for $C_{24}H_{27}FN_2O_4$ (426.48): C, 67.54; H, 6.33; **Found** (%): C, 67.27; H, 6.23.

Synthesiof1-4-{3-[4-(6-fluoro-benzo[d]isoxazol-3-yl)-piperidin-1-yl]-propoxy}-3-methoxy-benzaldehyde (Imp I)

4-(3-chloro-propoxy)-3-methoxy-benzaldehyde **10** (1.2 g, 52.47mmol) and 6-fluoro-3-piperidin-4-yl-benzo[d]isoxazole hydrochloride **7** (1.21g, 47.22mmol) were added to methanol (15 mL) and 2.0 mL of water at 25-30^{0}C. Diisopropylethylamine (2.71 g, 209.9mmol) was added to above suspension at ambient temperature. Slowly raised the reaction mass temperature up to 65-70^{0}C and maintained at the same temperature for 14h. The reaction progress was monitored by TLC (chloroform: methanol, 4:1). After completion of the reaction, the solvent was removed under reduced pressure below 65^{0}C and the product was purified by column chromatography, using ethyl acetate and n-hexane (7:1) to obtain 1.85g of the desired product as white solid (**Imp I**). (85.64% yields are based on the compound **10**). Purity by HPLC: 99.42%. **FTIR** (KBr, ν,cm^{-1}): 3030, 2948, 2778, 2744, 2820, 1680, 1612, 1583, 1509, 1459, 1446, 1414, 1381,1310, 1260, 1220, 1176, 1149, 1121, 1076, 1032, 995, 982, 953, 883, 875, 851, 810, 780, 642, 609, 568, 474; **^{1}H NMR** (400 MHz, $CDCl_3$):δ 2.03−2.10 (m, 6H), 2.12−2.18 (m, 2H, C-CH_2-C), 2.58−2.60 (t, 2H, N-CH_2-C),3.02−3.09 (m, 2H), 3.91 (s, 3H, Ar-OCH_3), 4.11−4.19 (t, 2H, , C-CH_2-OAr), 6.91−6.93 (d, 1H), 7.01−7.06 (dd, 1H), 7.21−7.24 (dd, 1H),7.51−7.52 (d, 1H), 7.53−7.56 (dd, 1H), 7.65−7.70 (dd, 1H).9.87(s,1H, AR-CHO); **^{13}C NMR** ($CDCl_3$): 30.32, 34.31, 53.34, 54.88, 55.78, 67.14, 97.01, 97.29, 110.18, 111.00, 111.96,112.20, 117.10, 122.34, 122.44, 123.02, 130.09, 148.00, 152.64, 160.89, 162.58, 163.51, 163.62, 165.04, 191.57, 194.5; **MS** (ESI, m/z): 413.2 [M + H]+; **Anal.Calcd** (%) for $C_{23}H_{25}FN_2O_4$ (412.45): C, 67.54; H, 6.33; **Found** (%): C, 67.22; H, 6.21

Synthesis of 4-(3-chloro-propoxy)-3-methoxy-benzaldehyde 10

To a stirred solution of 4-hydroxy-3-methoxy benzaldehyde **8** (7 g, 46.0mmol), acetonitrile (40mL) and potassium carbonate (15.23 g, 110.41mmol) were charged at room temperature. Toluene-4-sulfonic acid 3-chloro-propyl ester **4** (12.58 g, 50.60mmol) in acetonitrile (30 mL) was added drop wise at ambient temperature for 15 min and maintained at 65-70^{0}C for 3h. The reaction progress was monitored by TLC (methylene dichloride: methanol, 4:1). After completion of reaction, it was cooled to room temperature and filtered the salts. Solvent was removed from filtrate under reduced pressure below 60^{0}C and recrystallized from n-hexane (30mL) as a low melting light brown crystalline solid **10**. Formation of dimer impurity **10** was well controlled below 0.4% in **10** without high-vacuum distillation. (9.89 g obtained yield: 94 .01%) (99.15 % purity by HPLC), m.p.55-58^{0}C; **FT-IR** (KBr, ν,cm^{-1}): 3011, 2956, 2936, 2852, 2744,1680, 1596, 1584, 1508, 1465, 1454, 1422, 1354, 1275,1241, 1196, 1157, 1069, 1029, 863, 812, 753, 722; **^{1}H NMR**(400 MHz, $CDCl_3$): δ 2.31-2.34 (m, 2H, C-CH_2-C), 3.76-3.79 (t, 2H, J = 6.2 Hz, Cl-CH_2-C), 3.92 (s, 3H, Ar-OCH_3), 4.24-4.27 (t, 2H, J = 6.0 Hz, C-CH_2-OAr), 6.99-7.01 (d,1H, J = 8.1 Hz), 7.41-7.45 (m, 1H), 7.41-7.45 (m, 1H), 9.85 (s, 1H, AR-CHO.); **^{13}C NMR** ($CDCl_3$): 25.80, 31.69, 41.01,55.59, 65.10,109.26, 110.23, 121.80, 130.36, 148.88, 151.20, 191.11, 195.25; **MS** (ESI, m/z): 229.6 [M + H]+, 251.65 [M + Na]+. ; **Anal.Calcd**. (%) for $C_{11}H_{13}ClO_3$ (228.66): C, 59.39; H, 6.23; **Found** (%): C, 59.22; H, 6.14.

Synthesis of 6-fluoro-3-{1-[3-(2-methoxy-phenoxy)-propyl]-piperidin-4-yl}-benzo[d]isoxazole (Imp II)

1-(3-chloro-propoxy)-2-methoxy-benzene **11** (0.5 g, 24.91mmol) and 6-fluoro-3-piperidin-4-yl-benzo[d]isoxazole hydrochloride **7** (0.57 g, 22.42mmol) were added to methanol (70mL) and 1.0 mL of water at 25-30^{0}C. Diisopropylethylamine (1.28 g, 99.67mmol) was added to above suspension at ambient temperature. The reaction temperature increased slowly up to 65-70^{0}C and maintained at the same temperature for 16h. The reaction progress was monitored by TLC (chloroform: methanol, 4:1). After completion of reaction, the solvent was removed under reduced pressure below 65^{0}C and the product was purified by column chromatography with eluent system of ethyl acetate and n-hexane (7:1) to obtain 0.82 g of the target product as white solid (**Imp II**). (85.68% yields are based on compound **11**). Purity by HPLC: 99.40%. **FT-IR** (KBr, ν , cm^{-1}): 3069, 2932, 2841, 2768, 2746, 1613, 1590, 1508, 1469, 1454, 1416, 1387, 1313, 1257, 1226, 1817, 1151, 1123, 1091, 1054, 987, 967, 956, 907, 879, 857, 817, 780, 653, 620, 529, 462.; **^{1}H NMR** (400 MHz, $CDCl_3$):δ 2.06−2.15 (m, 6H), 2.18−2.21 (m, 2H), 2.60−2.64 (t, 2H), 3.09−3.11 (m, 2H), 3.86 (s, 3H), 4.10−4.19 (t, 2H), 6.88−6.90 (m, 2H), 6.91−6.92 (dd, 2H) 7.02-7.07 (m, 1H.), 7.22−7.26 (dd, 1H), 7.69−7.72 (dd, 1H); **^{13}C NMR** ($CDCl_3$): 30.34, 34.34, 53.36, 54.90, 55.80, 67.16, 97.04, 97.31, 110.20, 111.02, 111.98, 112.23, 117.12, 122.36, 122.46, 123.06, 130.11, 152.66, 160.91, 162.60, 163.53, 163.64, **MS** (ESI, m/z): 385.2 [M + H]+. **Anal.Calcd** (%) for $C_{22}H_{25}FN_2O_3$ (384.24): C, 67.54; H, 6.33; **Found** (%): C, 67.43; H, 6.25.

Synthesis of 1-(3-chloro-propoxy)-2-methoxy-benzene 11

To a stirred solution of 2-methoxy-phenol **9** (5 g, 40.27mmol), acetonitrile (30 mL) and potassium carbonate (13.33 g, 96.66mmol) were charged at room temperature. Toluene-4-sulfonic acid 3-chloro-propyl ester **4** (11.01 g, 44.30mmol) in acetonitrile (20mL) was added drop wise at ambient temperature for 20 min and maintained at 65-70^{0}C for 3h. The reaction progress was monitored by TLC (methylene

dichloride: methanol, 4:1). After completion of reaction, it was cooled to room temperature and filtered the salts. Filtrate was taken and the solvent was removed under reduced pressure below 60^0C and recrystallized from n-hexane (25mL) as a low melting white crystalline solid **11**. The formation of dimer impurity was well controlled below 0.3% in **11** without high-vacuum distillation. (7.55 g Yield: 93.44 %) (98.9 % Purity by HPLC), **FT-IR** (KBr ,ν , cm^{-1}): 3032, 2933, 2842, 2878, 1523, 1515, 1466, 1452, 1420, 1355, 1277,1225, 1182, 1146, 1077, 1034, 873, 806, 757, 722; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.28-2.36 (m, 2H, C-CH_2-C), 3.74-3.76 (t, 2H, J = 6.2 Hz, Cl-CH_2-C), 3.90 (s, 3H, Ar-OCH_3), 4.21-424 (t, 2H, J = 6.2 Hz, C-CH_2-OAr), 6.92-6.94 (dd, 1H, J = 8.1 Hz), 7.25-7.35 (m, 2H), 7.53-7.58 (m, 1H); **^{13}C NMR** ($CDCl_3$): 25.80, 31.70, 41.06, 55.61, 65.10, 110.23, 111.20, 122.80, 130.33, 148.92, 152.20; **MS** (ESI, m/z): 201.6 [M + H] +, 224 [M + Na]+.; **Anal. Calcd**. (%) for $C_{10}H_{13}ClO_2$ (200.66): C, 59.39; H, 6.23; **Found** (%): C, 59.32; H, 6.16.

Synthesis of 1, 3-bis-(4-{3-[4-(6-fluoro-benzo[d]isoxazol-3-yl)-piperidin-1-yl]-propoxy}-3-methoxy-phenyl)-propenone (Imp III)

Route 1: A solution of 30%NaOH (10mL) was added to a vigorously stirring solution of the mixture of 1-(4-{3-[4-(6-fluoro-benzo[d]isoxazol-3-yl)-piperidin-1-yl]-propoxy}-3-methoxy-phenyl)-ethanone **1** (0.80 g, 18.75mmol) and 4-{3-[4-(6-fluoro-benzo[d]isoxazol-3-yl)-piperidin-1-yl]-propoxy}-3-methoxy-benzaldehyde (**Imp I**) derivative (0.77 g, 18.75mmol) in ethanol (20 mL). The resultant solution was then stirred at room temperature for 2h and was heated under reflux for further 8h. After TLC check, the reaction mixture was diluted with EtOAc, neutralized with HCl solution (10%), and then washed with water. The organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated to get solid compound. The solid compound was recrystallized in EtOAc/n-hexane (1:9) to give 0.4 g of the title compound **Imp III** as base form. (26.14% yield). Purity by HPLC: 99.42%.

Route 2: To a mixture of con. HCl (10mL) in water (5mL) and 50 mg of p-toluene sulfonic acid (p-TSA) catalyst were added to a vigorously stirring solution of the mixture of 1-(4-{3-[4-(6-fluoro-benzo[d]isoxazol-3-yl)-piperidin-1-yl]-propoxy}-3-methoxy-phenyl)-ethanone **1**(1.0 g, 23.44mmol) and 4-{3-[4-(6-fluoro-benzo[d]isoxazol-3-yl)-piperidin-1-yl]-propoxy}-3-methoxy-benzaldehyde (**Imp I**) derivative (0.96 g, 23.44mmol) in ethanol (30mL). The resultant solution was then stirred at room temperature for 1h and was heated up to 80-85^0C and maintained at the same temperature for further 10h until solid mass was formed. Reaction completion was ensured with TLC examination, and then it was quenched into ice water and acidified with 10 % HCl and obtained the product (title compound **Imp III**), filtered, dried in a hot air oven and weighed. The crude product was further recrystallized using ethanol to yield final product as yellow solid in hydrochloride salt form. (0.95 g, 49.47% yield). Purity by HPLC: 99.42%. **FT-IR** (KBr, ν , cm^{-1}): 3039, 2949, 2779,2746, 1652, 1613, 1585, 1510, 1462, 1448, 1415, 1380,1313, 1262, 1221, 1177, 1150, 1123, 1071, 1028, 997, 985, 955,893, 876, 853, 815, 721, 648, 610, 568, 476.; **^{1}H NMR** (400 MHz, DMSO-d_6): δ 1.33-1.35 (m, 6H), 2.21−2.32 (m, 4H), 3.17-3.26 (m 4H), 3.46-3.48 (m, 4H), 3.47-3.51 (m, 4H), 3.67−3.88 (m, 4H), 3.96 (s, 3H), 3.98 (s, 3H), 4.15−4.22 (t, 2H), 4.24−4.26 (t, 2H), 7.06−7.08 (d, 1H), 7.14−7.16 (d, 1H), 7.23−7.26 (dd, 1H), 7.47-7.62 (dd, 1Hx2), 7.55−7.62 (d, 1H), 7.55−7.62 (dd, 1H), 7.63-7.65 (dd, 1Hx2), 7.70−7.74 (d, 1H J=16), 7.89-7.91 (dd, 1H, J=8.0), 7.84-7.88 (d, 1H, J= 16) , 7.93-7.95 (d, 1Hx2,), 11.11(s, broad, 2x1H, HCl.) ; **^{13}C NMR** (DMSO-d_6): 23.63, 26.88, 31.23, 39.91, 51.36, 53.44, 55.71, 55.90, 66.16, 66.26, 97.04, 97.29, 97.56, 110.99, 111.40, 112.01, 112.54, 112.80, 112.99, 116.74, 119.77, 123.29, 123.46, 123.87, 123.97, 128.06, 131.00, 143.53, 148.89, 149.17, 150.05, 152.08, 160.16, 162.46, 163.10, 163.25, 164.93, 187.52. **MS** (ESI, m/z): 821.4 [M + H] +, [M-411] +. **Anal.Calcd** (%) for $C_{47}H_{50}F_2N_4O_7$ (820.92): C, 67.08; H, 5.79; N, 13.41%; **Found**: C, 67.0; H, 5.71; N, 13.40%.

Route 3: 1, 3-bis-[4-(3-chloro-propoxy)-3-methoxy-phenyl]-propenone **12** (1.0 g, 2.20mmol) was added to DMF (20 mL) followed by successive addition of 6-chloro-3-piperidin-4-yl-benzo[d]isoxazole hydrochloride **7** (1.18g, 4.63mmol), potassium carbonate (1.36 g, 9.92mmol) and potassium iodide (25 mg, catalytic amount) at 25-30^0C. The reaction mass was maintained at 95-100^0C for 9h under nitrogen atmosphere. Completion of the reaction was monitored by TLC and reaction mass was cooled to 25-30^0C and filtered off precipitated salts. The filtrate was distilled under reduced pressure up to a mass volume of ~10mL. The contents are cooled to 0-5^0C and filtered off product and washed with pre cooled methanol (2x5mL, 2-8^0C) to give compound **Imp III** as yellow crystals (1.5 g,); (82.87% yield). Purity by HPLC: 99.38%. **FT-IR** (KBr , ν, cm^{-1}): 3076, 2937, 2686, 2632, 2511, 1652, 1613, 1594, 1514, 1467, 1420, 1380, 1312, 1262, 1221, 1177, 1150, 1123, 1071, 1028, 972, 955, 893, 836, 815,758, 648, 610, 568, 476.; **^{1}H NMR** (400 MHz, DMSO-d_6): δ 1.33-1.35 (m, 6H), 2.15−2.24 (m, 4H), 3, 2-3.26 (m 4H), 3.46-3.48 (m, 4H), 3.49-3.51 (m, 4H), 3.77−3.80 (m, 4H), 3.96 (s, 3H), 3.98 (s, 3H), 4.22−4.23 (t, 2H), 4.24−4.26 (t, 2H), 7.06−7.09 (d, 1H), 7.14−7.16 (d, 1H), 7.23−7.26 (dd, 1H), 7.47-7.62 (dd, 1Hx2), 7.53−7.61 (d, 1H), 7.53−7.61 (dd, 1H), 7.63-7.65 (dd, 1Hx2), 7.70−7.74 (d, 1H J=16), 7.89-7.91 (dd, 1H, J=8.0.).7.92-7.94 (d, 1H, J= 16) 7.95-7.96 (d, 1Hx2,); **^{13}C NMR** (DMSO-d_6): 23.63, 26.88, 31.23, 38.87, 40.13, 51.34, 53.44, 55.71, 55.90, 66.16, 66.26, 97.29, 97.56, 110.99, 111.4, 111.98, 112.01, 112.54, 112.80, 112.99, 116.74, 119.77, 123.29, 123.46, 123.87, 123.97, 128.06, 131.00, 143.53, 148.89, 149.17, 150.05, 152.08, 160.16, 162.46, 163.10, 163.25, 164.93, 187.32; **MS** (ESI, m/z): 821.4 [M + H]+, [M-411]+. **Anal.Calcd** (%) for $C_{47}H_{50}F_2N_4O_7$ (820.92): C, 67.08; H, 5.79; N, 13.41%; **Found**: C, 67.12; H, 5.71; N, 13.39.

Synthesis of 1, 3-bis-[4-(3-chloro-propoxy)-3-methoxy-phenyl]-propenone 12

A solution of 30% NaOH (10mL) was added to a vigorously stirring solution of the mixture of 1-[4-(3-chloro-propoxy)-3-methoxy-phenyl]-ethanone **6** (0.6 g, 24.72mmol) and 4-(3-chloro-propoxy)-3-methoxy-benzaldehyde **10** derivative (0.56 g, 24.72mmol) in ethanol (20mL). The resultant solution was then stirred at room temperature for 2h and was heated under reflux (85^0C) for further 5huntil the entire mixture becomes very cloud then the mixture was poured slowly into 20mL of water with constant stirring and kept in refrigerator for 24 h. The reaction was monitored by TLC (ethyl acetate: n-hexane) (4:2). The reaction is neutralized by glacial acetic acid and the yellow crystalline precipitate obtained was filtered, washed and recrystallized from ethanol. (1.02 g, 91.07% yield). Purity by HPLC: 98.42%. **FT-IR** (KBr, ν, cm^{-1}): 3079, 2932, 2876, 1651, 1595, 1511, 1466, 1421, 1347, 1310, 1263, 1196, 1168, 1142, 1031, 978, 948, 908, 889, 845, 797,774, 654, 639, 572,

470; **^{1}H NMR** (400 MHz, DMSO-d_6): δ 2.15−2.24(m, 4H), 3.77-3.80(m, 4H), 3.811(s, 3H), 3.82(s, 3H), 4.13−4.16(t, 2H), 4.19−4.22(t, 2H), 7.03−7.05(d, 1H), 7.11−7.14(d, 1H), 7.38−7.40(dd, 1H), 7.52−7.53(d, 1H), 7.60−7.61(d, 1H), 7.65−7.69(d, 1H J=16), 7.81-7.85(d, 1H, J= 16) 7.89-7.91(dd, 1H, J=8.0.). **^{13}C NMR** (DMSO-d_6): 30.36, 34.34, 53.36,54.90, 55.80, 67.16, 97.04, 97.31, 110.20, 111.02, 111.98,112.23, 117.12, 122.36, 122.46, 123.06, 130.11, 142.89, 148.00, 152.66, 160.91, 162.60, 163.53, 163.66, 165.09, 189.59. **MS** (ESI, m/z): 454.3 [M + H] +,[M-227.3] +. **Anal.Calcd** (%) for $C_{23}H_{26}Cl_2O_5$ (453.36): C, 67.54; H, 6.33; **Found** (%): C, 67.17; H, 6.05.

Synthesis of 1-(4-{3-[4-(6-fluoro-benzo[d]isoxazol-3-yl)-3, 6-dihydro-2H-pyridin-1-yl]-propoxy}-3-methoxy-phenyl)-ethanone (Imp IV)

A mixture of commercial-grade pyridiniumchlorochromate (7.22 g, 33.4mmol) was grounded to a fine powder using a mortar and pestle. The powder was added in to 100 mL of methylene chloride equipped with a 500 mL round-bottom flask. To this, the orange suspension, 1-(4-{3-[4-(6-fluoro-benzo[d]isoxazol-3-yl)-3, 6-dihydro-2H-pyridin-1-yl]-propoxy}-3-methoxy-phenyl)-ethanol **20** (6.5 g, 15.2mmol) was added in one portion and stirred. The solution darkened within 30 min and the reaction mixture was stirred well at ambient temperature for 3 hunder nitrogen atmosphere. The reaction was monitored by TLC (hexane/ethyl acetate, 1:4); the reaction mixture was diluted with ethyl acetate (150 mL) and filtered under vacuum using a Buchner funnel (75mm) layered with celite/hyflow bed (2 cm). The filtrate was concentrated under vacuum and the resulting residue was diluted with ethyl acetate (100 mL), washed with water (2x50 mL), and finally washed with saturated aqueous sodium chloride (50mL). The organic layer was then dried over anhydrous sodium sulfate (10 g) and the drying agent was removed by suction filtration. Concentration of the ethyl acetate solution under vacuum afforded as a yellow gummy mass. The technical product was further purified by column chromatography, eluent system being ethyl acetate and n-hexane (7:1) to obtain 3.2 g of title product (**Imp IV**) as white solid. Yield: 49.53%. **FT-IR** (KBr, ν, cm^{-1}): 3454, 3076, 2994, 2959, 2856, 2831, 1732, 1666, 1596, 1584, 1511, 1495, 1473, 1457, 1370, 1341, 1270, 1222, 1181, 1147, 1131, 1076, 1057, 1015, 985, 958, 931, 876, 857, 831, 763, 683, 651, 568, 475.; **^{1}H NMR** (400 MHz, DMSO-d_6): δ 1.94-2.02 (m, 2H,-C-CH_2 – C), 2.52 (s, 3H, CO-CH_3), 2.53−2.77 (m, 6H, CH_2-Pyrid), 3.32−3.34 (m, 2H, N-CH_2.), 3.82 (s, 3H,O-CH_3.), 4.11-414 (m, 2H,ArO-CH_2) ,6.89 (Sa, 1H, H-C=C Pyrid), 7.06−7.08 (d, 1H,AV), 7.30-7.32 (dd ,1H, AV.), 7.34-7.44 (dd, 1H, AV.), 7.59−7.61 (ddd, 1H , AR), 7.73−7.75 (dd, 1H, AR.), 8.14−8.18 (dd, 1H, AR.); **^{13}C NMR** (DMSO-d_6): 26.07, 26.60, 27.01, 49.48, 52.96, 54.46, 55.91, 67.13, 76.68, 77.00, 77.31, 97.13, 97.39, 110.41, 111.22, 112.57, 112.81, 116.40, 123.11, 123.20, 123.31, 126.80, 129.6, 130.32, 149.14, 152.72, 156.29, 162.47, 163.93, 164.07, 164.96, 196.66. **MS** (ESI, m/z): 425.2 $[M + H]^+$; **Anal.Calcd** (%) for $C_{24}H_{25}FN_2O_4$ (424.46): C, 67.94; H, 6.32; **Found** (%): C, 67.30; H, 6.22.

Synthesis of 1-(4-{3-[4-(6-fluoro-benzo[d]isoxazol-3-yl)-3, 6-dihydro-2H-pyridin-1-yl]-propoxy}-3-methoxy-phenyl)-ethanol 20

3.11 g (0.082mol) of $NaBH_4$ was added portion-wise over a suspension of 25g (0.045mol) of the compound **19** in methanol (250 mL), at the temperature 0-5^{0}C. At the end of the addition, the reaction mixture was stirred for further 30 min and 24.33 g (0.45mol) of NH_4Cl was added. The reaction progress was monitored by TLC (chloroform: methanol 4:1); the solvent (MeOH) was removed by evaporation at 50^{0}C under reduced pressure to obtain the residual mass. It was cooled to room temperature and then added 75 mL of water 5mL of con. HCl to adjust pH in between 3-4 and extracted with ethyl acetate (2 x 150 mL). The combined organic layer was washed with brine solution (2x200 mL), water (2 x75 mL) and dried over anhydrous sodium sulphate and concentrated under reduced pressure. The residue was purified by column chromatography (20% EtOAc in n-hexane) to obtain **20** as white solid. (7.5 g, yield: 38.58%). **FT-IR** (KBr, ν , cm^{-1}): 3401, 3031, 2949, 2779, 2746, 2822, 1680, 1614, 1585, 1510, 1462, 1448, 1415, 1380, 1313, 1262, 1221, 1177, 1150, 1123, 1077, 1034, 997, 985, 955, 884, 876, 853, 812, 781, 643, 610, 569, 475; **^{1}H NMR** (400 MHz, DMSO-d_6): δ 1.28-1, 29 (d, 3H), 1.89-1.94 (m, 2H,-CH_2) , 2.57−2.68 (m, 2H), 2.74−2.80 (m, 4H), 3.22−3.49 (m, 2H, N-CH_2), 3.75 (s, 3H,O-CH_3), 3.97−4.00 (m, 2H,O-CH_2), 4.61-4.66 (qtr., 1H) ,6.79 (Sa, 1H, H-C=C Pyrid), 6.814−6.87 (dd, 1H , AV), 6.87-6.89 (dd ,1H, AV.), 6.88-6.94 (d, 1H, AV.), 7.288−7.33 (ddd, 1H), 7.72−7.74 (dd, 1H,AR), 8.0 (s, broad, 1H, secondary O-H), 8.14−8.17 (dd, 1H, AR.); **^{13}C NMR** ($CDCl_3$): 26.02, 26.40, 30.36, 34.34, 53.36, 54.90, 55.80, 67.16, 97.04, 97.31, 110.20, 111.02, 111.98, 112.23, 117.12, 122.36, 122.46, 123.06, 130.11, 141, 149.00, 152.66, 160.91, 162.60, 163.53, 163.66, 165.09, 198.56. **MS** (ESI, m/z): 427.2 [M + H] +.

Synthesis of 1-[3-(4-acetyl-2-methoxy-phenoxy)-propyl]-4-(6-fluoro-benzo[d]isoxazol-3-yl)-pyridinium; iodide 19

1-[4-(3-chloro-propoxy)-3-methoxy-phenyl]-ethanone **6** (23.79 g, 0.098mol) and 6-fluoro-3-pyridin-4-yl-benzo[d]isoxazole **18** (20 g, 0.093mol) were added to DMF (30mL) and 120 mL of acetonitrile at 25-30^{0}C. Potassium iodide (17.04 g, 0.102mol) was added to above suspension at ambient temperature. Slowly raised the reaction mass temperature up to 65-70^{0}C and maintained at the same temperature for 10 h. The reaction progress was monitored by TLC (chloroform: methanol, 4:1); after completion of reaction, light yellow colored solid mass was formed, the reaction mass was kept at room temperature and cooled to 10^{0}C, stirred well at same conditions for 1h. Then it was filtered and washed with acetonitrile (25 mLx2), after drying under vacuum for 3h at 55^{0}C to obtain as a yellow crystalline solid of the title compound **19**. The crude product was used in the next step without further purification. (48.8 g, 95.3% yield). M.p:155-160^{0}C**, FT-IR** (KBr, ν, cm^{-1}): 3031, 2949, 2779, 2746, 2822, 1630, 1614, 1585, 1510, 1462, 1448, 1415, 1380, 1313, 1262, 1221, 1177, 1150, 1123, 1077, 1034, 997, 985, 955, 884, 876, 853, 812, 781, 643, 610, 568, 472. **^{1}H NMR** (400 MHz, DMSO-d_6): δ 2.76−2.77 (s, 3H, $COCH_3$), 3.04-3.25 (m, 2H, C-CH_2), 3.44-3.55 (s, 3H, Ar-OCH_3), 4.05-4.28 (m,2H, Ar-O-CH_2), 4.94-4.95 (m, 2H, N-CH_2), 7.05−7.05 (d,1H, J=8.0, 4.0, 1H, AR), 7.31 (dd, 1H,AR.), 7.56-7.58 (dd, J=8.0, 4.0, 1H, AR), 7.59−7.61 (dt, J=3.6, 9.6, 1H,AR) 8.04−8.06 (dd, J=3.6, 8.5, 1H,AR), 8.38−8.40 (dd, J=5.2, 9.6, 1H,AR.) 8.79−8.81 (d, J=6.0, 2H, Pyrid.), 9.39−9.40 (d, J=6.0, 2H, Pyrid.); **^{13}C NMR** (DMSO-d_6): 26.02, 26.40, 30.36, 34.34, 53.36, 54.90, 55.80, 67.16, 97.04, 97.31, 110.20, 111.02, 111.98, 112.23, 117.12, 122.36, 122.46, 123.06, 130.11, 143.55, 152.66, 160.91, 162.60, 163.53, 163.66,

165.09, 199.59. **MS** (ESI+/-, m/z): 548.35 [M-H] + and 420.32 [M-127] +.

Synthesis of 6-fluoro-3-pyridin-4-yl-benzo[d]isoxazole 18

181 g,(0.773 mol) of the oxime E/Z mixture of compound **17** in 600 mL of ethanol were added in portion to 77.3 g(1.94 mol)of NaOH and 180 mL of water solution at ambient temperature for 30 min and the reaction mass was heated up to 85-90^{0}C and maintained the reaction mass at the same temperature for 4h. The reaction progress was monitored by TLC (n-hexane: ethylacetate, 3:2), the solvent (EtOH) was removed by evaporation at 55^{0}C under reduced pressure to obtain the residual mass. It was cooled to room temperature and then added 800 mL of water, extracted with ethylacetate (2x500 mL). The combined organic layer was washed with brine solution (2x200 mL), water (2x200 mL) and dried over anhydrous sodium sulphate and concentrated under reduced pressure. The residual mass was recrystallized from methanol twice to obtain 53g of the title product **18** as a white solid. Yield: 32 %. Melting Range: 138-146^{0}C; **FT-IR** (KBr, ν, cm^{-1}): 2952, 2853, 1618, 1556, 1516, 1492, 1484, 1415, 1373, 1317, 1270, 1222, 1177, 1140, 1117, 1064, 1007, 992, 957, 892, 839, 812, 763, 682, 671, 547, 470. **^{1}H NMR** (400 MHz, DMSO-d_6): δ 7.42−7.47 (m, 1H, AR.), 7.89−7.92 (m, 1H, AR), 8.00−8.28 (m, 3H, AR. and Pyrid.), 8.84−8.85 (m, 2H, Pyrid.) **MS** (ESI, m/z): 215.1 [M + H] +.

Synthesis of (2, 4-difluoro-phenyl)-pyridin-4-yl-methanone oxime 17

62.6 g, (0.9mol) of hydroxylamine hydrochloride and 133.6g (0.982mol) sodium acetate tri hydrate were added to a suspension of 179.4g (0.818mol) of compound **16** in 600 mL of ethanol and the mixture was refluxed for 1h. The solvent (EtOH) was removed by evaporation at 55^{0}C under reduced pressure to obtain the residual mass. The reaction progress was monitored by TLC (methylene dichloride: methanol, 4:1) after completion of reaction, it was cooled to room temperature and then added 1L of water, was stirred for 30 min at room temperature until solid formed. It was filtered, dried for 3h at 45^{0}C to obtain compound **17** as white solid (181 g mixture of Syn-and Anti-isomers of oxime). The crude material was used in the next step without further purification. (94% yield). Melting range: 155-200^{0}C, **FT-IR** (KBr, ν, cm^{-1}): 2947, 2776, 2746, 282, 1580, 1510, 1462, 1448, 1415, 1380, 1313, 1262, 1221, 1177, 1150, 1123, 1077, 1034, 997, 985, 955, 884, 876, 853, 812, 781, 643, 610, 569, 475**; ^{1}H NMR** (400 MHz, DMSO-d_6): δ 7.10−7.70 (m, 5H, AR. and Pyrid), 8.85−8.80 (m, 2H Pyrid.), 12.40 (s and a,1H,-OH), **MS** (ESI, m/z): 235.19 [M + H]+, 257.20 [M + Na]+.

Synthesis of (2, 4-difluoro-phenyl)-pyridin-4-yl- methanone 16

219 mL (3.0mol) of thionyl chloride was added to a solution of 246.2 g (2.0mol) of isonicotinic acid **13** in 500 mL of 1, 2-dichloroethane and the mixture was refluxed for 4h. The excess thionyl chloride and the EDC were removed by evaporation at 55^{0}C under reduced pressure to obtain the residual mass. Then 392 mL (4.0mol) of 1, 3-diflourobenzene was added to 533 g (4.0mol) of $AlCl_3$ portion wise for 10 min. Exothermic reaction was observed. Once the exothermal reaction has ends, the reaction mixture was refluxed for 5h. The reaction progress was monitored by TLC (methylene dichloride: methanol, 4:1) after completion of reaction, it was cooled to room temperature and poured over a mixture of 3 kg ice and 1 kg of water, stirred for 30 min and the two phases were separated. The aqueous phase was washed with 1 L of EDC, basified with 2L of 40% NaOH solution and extracted the product with dichloromethane (2 x 1L). The combined organic layer was washed with brine solution (1L), dried over anhydrous sodium sulphate and concentrated under reduced pressure to give as an ochre colored oil of title compound **16** (179.4 g). The crude product was used as such in the next step without further purification. (41% yield). **FT-IR** (KBr, ν, cm^{-1}): 2949, 2779, 2746, 282, 1680, 1585, 1510, 1462, 1448, 1415, 1380, 1313, 1262, 1221, 1177, 1150, 1123, 1077, 1034, 997, 985, 955, 884, 876, 853, 812, 781, 643, 610, 569, 475; **^{1}HNMR** (400 MHz , $CDCl_3$): δ 6.88−7.12 (m, 2H,AR.), 7.56−7.61 (m, 2H, Pyrid.), 7.64−7.77 (m, 1H,AR.), 8.81−8.85 (m, 2H,Pyrid.); **MS** (ESI, m/z): 220.17 [M + H]+.

Synthesis of 1-[4-(3-{4-[(2, 4-difluoro-phenyl)-hydroxyimino-methyl]-piperidin-1-yl}-propoxy)-3-methoxy-phenyl]-ethanone (Imp V)

1-[4-(3-chloro-propoxy)-3-methoxy-phenyl]-ethanone **6** (1.2 g, 49.44mmol) and of 1 (2, 4-difluoro-phenyl)-piperidin-4-yl-methanone oxime hydrochloride **26** (1.07 g, 44.49mmol) were added to methanol (30 mL) and 5 mL of water at 25-30^{0}C. Diisopropyl ethyl amine (2.55 g, 197.77mmol) was added to above suspension at ambient temperature. Slowly raised the reaction temperature up to 65-70^{0}C and maintained at the same temperature for 16h. The reaction progress was monitored by TLC (chloroform: methanol, 4:1), the solvent was removed under reduced pressure below 65^{0}C and the technical product was further purified by column chromatography, eluent system being ethyl acetate and n-hexane (7:1) to obtain 1.11 g of the title product as white solid (**Imp V**). (50.45% yield based on compound **6** (98.99 % purity by HPLC), **FT-IR** (KBr, ν, cm^{-1}): 3441, 3178, 3075, 2957,2939, 2851, 2795, 1672, 1614, 1587, 1511, 1468, 1418, 1380, 1358, 1271, 1220, 1178, 1151, 1137, 1080, 1027, 964, 876, 859, 803, 789, 739, 669, 642, 569, 475.; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.82−1.84 (m, 6H), 2.05−2.07 (m, 2H), 2.55 (s, 3H), 2.58−2.60 (t, 2H), 3.06−3.10 (m, 3H), 3.88 (s, 3H), 4.06−4.09 (t, 2H), 6.79−6.82 (d, 1H), 6.82−6.84 (dd, 1H), 6.87−6.91 (dd, 1H) , 7.15-7.17(dd, 1H,), 7.47−7.49 (d, 1H), 7.47−7.49 (dd, 1H), 10.2 (s and a, 1H, oxime -OH). **^{13}C NMR** ($CDCl_3$): 26.06, 26.40, 30.36, 34.34, 53.36, 54.90, 55.80, 67.16, 97.04, 97.31, 110.20, 111.02, 111.98, 112.23, 117.12, 122.36, 122.46, 123.06, 130.11, 149.00, 152.66, 160.91, 162.60, 163.53, 163.66, 165.09, 198.52; **MS** (ESI, m/z): 447.2 [M + H]+, 469.2 [M + Na]+; **Anal.Calcd** (%) for $C_{24}H_{28}F_2N_2O_4$ (446.20) C, 67.08; H, 5.79; N, 13.41%; **Found**: C, 67.05; H, 5.75; N, 13.38%.

Synthesis of 1 (2, 4-difluoro-phenyl)-piperidin-4-yl-methanone oxime hydrochloride 26

4.7 g, (0.11mol) of NaOH and 45 mL water were added to a suspension of 16 g (0.056 mol) of the 1-{4-[(2,4-difluoro-phenyl)-hydroxyimino-methyl]-piperidin-1-yl}-ethanone **25** in 60 mLof ethanol and the mixture was refluxed for 5h. The completion of reaction was confirmed by TLC (methylene dichloride: methanol, 4:1), the solvent (EtOH) was removed by evaporation at 55^{0}C under reduced pressure to obtain the residual mass. Then it was cooled to room temperature and added 50 mL of water and 15 mL of conc. HCl, 50 mL of IPA, were refluxed for 1h till solid formed. It was cooled to below 10^{0}C and maintained for 30 min, filtered and after drying for

3h at 45^{0}C to obtain desired compound **26** as a white solid (7.2 g) (mixture of Syn and Anti isomers of oxime). The residue product was used in the next step without further purification. (45.91% yields). **FT-IR** (KBr, ν, cm^{-1}): 3291, 3077, 2952, 2924, 2746, 2830, 2743, 1612, 1594, 1498, 1448, 1420, 1388, 1371, 1266, 1218, 1158, 1158, 1136, 1085, 1056, 973, 964, 929, 908, 872, 856, 820, 808, 774, 664, 609, 574, 470. **^{1}H NMR** (400 MHz, DMSO-d$_6$): δ 1.95−1.99 (m, 4H), 2.14−2.19 (m, 4H), 3.10−3.19 (m, 1H), 6.93−6.95 (d, 1H), 7.24−7.26 (dd, 1H), 7.78-7.856 (dd, 1H), 10.2 (s, 1H , NH) 11.19 (s, Broad, 1H, HCl), 12.30 (s and a, 1H, N-OH); **MS** (ESI, m/z): 241.21 [M + H]+, 263.21 [M + Na]+.

Synthesis 1-{4-[(2, 4-difluoro-phenyl)-hydroxyimino-methyl]-piperidin-1-yl}-ethanone 25

6.29 g (0.09mol) of hydroxylamine hydrochloride and 14 g (0.102mol) sodium acetate tri hydrate were added to a suspension of 22 g(0.082mol) of compound **24** in 80 mL of ethanol and the mixture was refluxed for 1h. The solvent (EtOH) was removed by evaporation at 55^{0}C under reduced pressure to obtain the residual mass. The reaction progress was monitored by TLC (methylene dichloride: methanol, 4:1) after completion of reaction, it was cooled to room temperature and then added 100 mL of water, continued stirring for 30 min at room temperature till solids forms. It was filtered and dried for 3h at 45 ^{0}C to obtain white solid of title compound **25** (17.1 g) (mixture of Syn and Anti isomers of oxime). The resulted product was used as such in the next step without further purification. (73.61% yield). M.R: 150-190^{0}C. **FT-IR** (KBr, ν, cm^{-1}): 3291.24, 2952, 2830, 2779, 2746, 1612, 1594, 1510, 1462, 1448, 1415, 1380, 1313, 1262, 1221, 1177, 1150, 1123, 1077, 1034, 997, 985, 955, 884, 876, 853, 812, 781, 643, 610, 569, 483.; **^{1}H NMR** (400 MHz, DMSO-d$_6$): δ 1.94−1.98 (m, 4H), 2.13−2.19 (m, 4H), 2.58 (s, 3H), 3.03−3.10 (m, 1H), 6.92−6.94 (d, 1H), 7.21−7.24 (dd, 1H), 7.79-7.85 (dd, 1H).12.40(s and a, 1H, N-OH). **MS** (ESI, m/z): 283.29 [M + H] +, 305.29 [M + Na] +.

Synthesis of1-[4-(2, 4-difluoro-benzoyl)-piperidin-1-yl]-ethanone 24

30.6 g (0.3mol) of acetic anhydride was added to a solution of piperidine-4-carboxylic acid of 32.29 g **21** (0.25mol) in 120 mL of toluene portion wise for 30 min at ambient temperature. Reaction mass was refluxed for 2h and the excess acetic anhydride and toluene distilled under reduced pressure to obtain solid mass of **23** which dried on high vacuum for 10 min. 28.65 g (0.25mol) of thionyl chloride was added to a solution of 37.5 g (0.21mol) of 1-acetyl-piperdine-4-caroxylicacid **23** in 120 mL of 1, 2-dichloroethane and the mixture was stirred well at room temperature for 4h. The excess thionyl chloride and the EDC were removed by evaporation at 55^{0}C under reduced pressure to obtain the residual mass. To the 90.2 g (0.8mol) of 1, 3-diflourobenzene, 104.8 g (0.8mol) of $AlCl_3$was added in portion for 10 min. Once the exothermal reaction was completed, the reaction mixture was refluxed for 5 h. The reaction progress was monitored by TLC (methylene dichloride: methanol, 4:1) after completion of reaction, it was cooled to room temperature and poured over a mixture of 0.3 kg ice and 0.3 kg of water and continued stirring for 30 min and the two phases were separated. The aqueous phase washed with 250 mL of EDC, basified with 200 mL of 40% NaOH solution and extracted the product with dichloroethane (2x200 mL). The combined organic layer was washed with brine solution (200 mL), dried over anhydrous sodium sulphate and concentrated under reduced pressure to give a light brown colored oil of title compound **24** in 22 g. The crude material was used in the next step without further purification. (41.62% yield). **FT-IR** (KBr, ν, cm^{-1}): 2947, 2779, 2746, 1682, 1615, 1585, 1510, 1462, 1448, 1415, 1380, 1313, 1262, 1221, 1177, 1150, 1123, 1077, 1034, 997, 985, 955, 884, 876, 853, 812, 781, 643, 610, 569, 475. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.93−1.96 (m, 4H), 2.12−2.18 (m, 4H), 2.56 (s, 3H), 3.02−3.09 (m, 1H), 6.91−6.93 (d, 1H), (dd, 1H), 7.21−7.24 (dd, 1H), 7.69−7.65 (dd, 1H). **MS** (ESI, m/z): 268.27 [M + H] +.

Synthesis of [3-(6-fluoro-benzo[d]isoxazol-3-yl)-propyl]-(3-piperidin-4-yl-benzo[d]isoxazol-6-yl)-amine (Imp VI)

To a stirred solution of 6-fluoro-3-piperidin-4-yl-benzo[d] isoxazole **7** (3.0 g, 13.63mmol) in N, N-dimethyl form amide (20 mL) was charged with potassium hydroxide (1.07 g, 16.36mmol) at 25-30^{0}C. The reaction mixture was stirred at ambient temperature for 2h, and then slowly raised the reaction mass temperature up to 125-130 ^{0}C and maintained at the same temperature for 18-20 h under nitrogen atmosphere. The reaction progress was monitored by TLC (chloroform: methanol, 4:1) after completion of reaction, it was cooled to room temperature and quenched with water (50 mL). The desired product was extracted twice using ethyl acetate (100 mL). Finally the combined ethyl acetate layer was washed with water (80 mL). The ethyl acetate layer was then concentrated by rotary evaporator at below 65^{0}C under reduced pressure to obtain a residue which is recrystallized from isopropyl alcohol (20 mL) under reflux and cool at below 2^{0}C to obtain a white crystalline wet solid. Obtained wet product was dried under vacuum at 50−55^{0}C for 1-2 h. Dried compound **Imp VI** weight is 2.4 g. (41.88% yield based on **7**) (99.35 % purity by HPLC). **FT-IR** (KBr, ν, cm^{-1}): 3442, 2944, 2819, 2736, 2502, 2054, 1617, 1590, 1515, 1498, 1445, 1417, 1383, 1319, 1272, 1226, 1170, 1134, 1122, 1040, 1014, 957, 864, 836, 823, 801, 764, 666, 620, 532, 475, 463; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.02−2.14 (m, 4H), 2.04-2.15 (m, 4H), 2.18−2.20 (m, 1H), 2.19−2.24 (m, 1H) , 3.04−3.11 (m, 2H, C-CH_2-N), 3.05-3.19 (m, 2H, C-CH_2-N),), 3.26-3.32 (m, 4H, C-CH_2-N), 3.92-3.95 (d, 1H,NH), 6.97−7.00 (d, 1H), 7.05−7.07 (dd, 1H), 7.08−7.10 (dd, 1H), 7.25−7.28 (d, 1H), 7.57−7.59 (dd, 1H), 7.65−7.69 (dd, 1H); **^{13}C NMR** ($CDCl_3$): 26.02, 26.40, 30.36, 34.34, 53.36, 54.90, 55.80, 67.16, 97.04, 97.31, 110.20, 111.02, 111.98, 112.23, 117.12, 122.36, 122.46, 123.06, 149.00, 152.66, 162.60, 163.53, 164.66, 165.09, **MS** (ESI, m/z): 421.1[M + H]+; **Anal. Calcd** (%) for $C_{24}H_{25}FN_4O_2$ (420.4): C, 67.08; H, 5.79; N, 13.41%; **Found**: C, 67.06; H, 5.74; N, 13.36%.

Synthesis of 1-{4-[3-(4-{6-[4-(6-fluoro-benzo[d]isoxazol-3-yl)-piperidin-1-yl]-benzo[d]isoxazol-3-yl}-piperidin-1-yl)-propoxy]-3-methoxy-}-ethanone (Imp VII)

Route 1: To a stirred solution of KOH (0.62 g, 95.35mmol) in water (25mL) was charged with 6-fluoro-3-piperidin-4-yl-benzo[d]isoxazole **7** (1.0 g, 45.4mmol) at 25-30^{0}C. The reaction mixture was stirred at ambient temperature for 30 min and then heated to 50-55 ^{0}C; Iloperidone **1**(1.93 g, 45.4mmol) was added drop-wise. Slowly raised the reaction mass temperature up to 100-102^{0}C and maintained at the same temperature for 20-22 h. The reaction progress was monitored by TLC (chloroform: methanol, 4:1), after completion of

reaction, it was cooled to room temperature and diluted with water (40mL). The desired product was extracted twice using ethyl acetate (80mL). Finally, the combined ethyl acetate layer was washed with brine solution (80mL). The ethyl acetate layer was concentrated by rotary evaporator at below 65^0C under reduced pressure to obtain desired product and purified by column chromatography using eluent system of chloroform and methanol (9:1) to get dry compound **Imp VII** of 1.57 g, yield: 55.28 %.

Route 2: 1-[4-(3-chloro-propoxy)-3-methoxy-phenyl]-ethanone**6** (1.0 g, 41.20mmol) was added to N, N-dimethyl form amide (25 mL) followed by successive addition of [3-(6-fluoro-benzo[d]isoxazol-3-yl)-propyl] -(3-piperidin-4-yl-benzo[d] isoxazol-6-yl)-amine (**Imp VI**) (1.5 g, 37.08mmol), potassium carbonate (1.19 g, 86.52mmol) and potassium iodide (30 mg, catalytic amount) at 25-30^0C. The reaction was maintained at 95-100^0C for 9 h under nitrogen atmosphere. The reaction progress was monitored by TLC (chloroform: methanol, 4:1). After completion of reaction, it was cooled to room temperature and quenched with water (50 mL), desired product was extracted twice using ethyl acetate (50 mL). Finally the combined ethyl acetate layer was washed with water (80 mL). The ethyl acetate layer was then concentrated by rotary evaporator at below 60^0C under reduced pressure to obtain target product and was then recrystallized from isopropyl alcohol (30 mL) under reflux and cooled at below 2^0C to yield a white crystalline wet solid. Obtained wet product was dried under vacuum at 50-55^0C for 1-2 h. Dry weight of **Imp VII** was 1.6 g (62.01% yield based on **6**). (99.53 % purity by HPLC), **FTIR** (KBr, ν, cm^{-1}): 2944, 2944, 2819, 2735, 2502, 1617, 1590, 1515, 1498, 1445, 1417, 1350, 1319, 1272, 1243, 1226, 1170, 1134, 1122, 1103, 1014, 957, 985, 884, 836, 823, 801, 764, 666, 649, 533, 484.; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.04−2.10 (m, 6H), 2.10-2.13 (m, 4H), 2.18−2.20 (m, 1H), 2.19−2.24 (m, 1H) , 2.56 (s, 3H, $COCH_3$), 2.58−2.62 (t, 2H, N-CH_2-C), 3.04−3.11 (m, 2H, C-CH_2-N), 3.05-3.19 (m, 2H, C-CH_2-N), 3.27-3.32 (m, 2H, C-CH_2-N), 3.92 (s, 3H, Ar-OCH_3), 3.89-3.95 (m, 2H,), 4.18−4.21 (t, 2H, Ar-OCH_2), 6.92−6.94 (d, 1H), 6.97−6.99 (dd, 1H), 7.05−7.10 (dd, 2H), 7.26−7.28 (d, 1H), 7.53−7.55 (dd, 1H), 7.55−7.58 (dd, 2H), 7.65−7.69 (dd, 1H); **^{13}C NMR** ($CDCl_3$): 26.02, 26.40, 30.36, 34.34, 53.36, 47.23, 48.57, 54.90, 55.80, 67.16, 97.04, 97.31, 110.20, 111.02, 111.98, 112.23, 117.12, 122.36, 122.46, 123.06, 130.11, 149.00, 152.66, 160.91, 162.60, 163.53, 163.66, 165.09, 198.56; **MS** (ESI, m/z): 627.2 [M + H]+; **Anal.Calcd**(%) for $C_{36}H_{39}FN_4O_5$ (626.4) C, 67.08; H, 5.79; N, 13.41%; **Found**: C, 67.06; H, 5.76; N, 13.38%. HPLC retention time ~29.33 min.

Synthesis of 1-(4-{3-[4-(6-fluoro-benzo[d]isoxazol-3-yl)-piperidin-1-yl]-propoxy}-3-methoxy-phenyl)-ethanone N-oxide (Imp VIII)

Iloperidone **1** (5.0 g, 11.72mmol) was dissolved in methylene dichloride (60 mL) and it was cooled to 0^0C. Methyl trioxorhenium (0.029 g, 0.117mmol) and 30 mL of 30% hydrogen peroxide were added to the reaction mixture and it was stirred at 0^0C for 0.5 h. Further, temperature was raised to room temperature and stirred for 5h, then added a small portion of MnO_2 (10 mg), continued stirring for an additional 3 h. Reaction progress was monitored by TLC (n-hexane: ethyl acetate, 7:3). After completion of reaction, reaction mass was washed with 10 % $Na_2S_2O_3$ solution (60 mL) followed by saturated $NaHCO_3$ solution (60 mL) and pH between 8-9, 2x60 mL of water, 10 %NaCl solution (60 mL), dried on Na_2SO_4 (20 g), filtered the salt and evaporated solvent under vacuum at 50^0C. Light white coloured residue was obtained; it was recrystallized from isopropyl alcohol (20 mL) to yield a white coloured solid **Imp VIII (**3.9 g, 75.28 %). Purity by HPLC: 99.32%; m.p. 155-157^0C; **FT-IR** (KBr, ν, cm^{-1}): 3082, 2957, 2877, 1655, 1606, 1584, 1509, 1467, 1419, 1348, 1273, 1223, 1182, 1143, 1121, 1032, 971, 957, 881, 857, 813, 802; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.89−1.93 (m, 2H), 2.31−2.40 (m,2H), 2.55 (s, 3H), 2.60−2.72 (m, 2H), 3.29−3.52 (m, 2H), 3.29−3.52 (m, 2H), 3.29−3.52 (m, 2H), 3.29−3.52 (m, 1H), 3.85 (s, 3H), 4.23 (t, 2H, J = 6.0 Hz), 7.11 (d, 1H, J = 8.4 Hz), 7.30−7.36 (m, 1H), 7.62−7.65 (m, 1H), 7.71−7.74 (dd, J = 9.3 and 2.0 Hz, 1H), 8.02−8.07 (dd, J = 8.7 and 5.4 Hz, 1H); **^{13}C NMR** ($CDCl_3$) 22.13, 24.70, 26.35, 31.49, 55.54, 63.21, 67.07, 67.82, 97.51, 110.35, 111.86, 112.67, 123.11, 123.67, 129.95, 148.63, 152.22, 160.79, 163.10, 163.69, 196.40; **MS** (ESI, m/z): 443 [M+H]+. **Anal.Calcd**. (%) for $C_{24}H_{27}N_2O_5F$ (442.19): C, 65.15; H, 6.15; N, 6.33; **Found** (%): C, 65.09; H, 6.07; N, 6.28; HPLC retention time ~9.24 min.

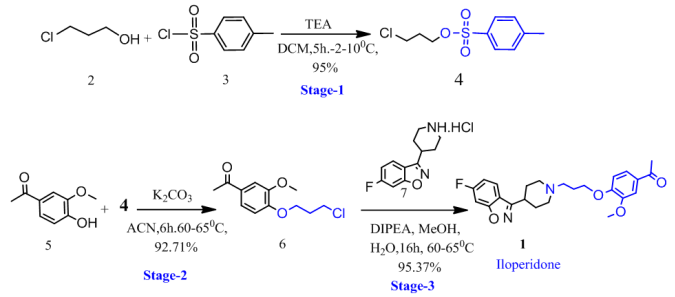
Synthesis of 1-{4-[3-(4-benzo[d]isoxazol-3-yl-piperidin-1-yl)-propoxy]-3-methoxy-phenyl}-ethanone (Imp IX)

1-[4-(3-chloro-propoxy)-3-methoxy-phenyl]-ethanone **6** (3.0 g, 12.36mmol) and 3-(4-piperidinyl)-1, 2-benzisoxazole mono hydrochloride **28** (2.65 g, 11.66mmol) were added to methanol (40mL) and 1.0 mL of water at 25-30^0C. Diisopropyl ethyl amine (6.39 g, 49.44mmol) was added to above suspension at ambient temperature. Slowly raised the reaction mass temperature up to 62-65^0C and maintained at the same temperature for 14 h. The reaction progress was monitored by TLC (chloroform: methanol, 4:1) after completion of reaction, the solvent was removed under reduced pressure below 65^0C and recrystallized from isopropyl alcohol (20mL) under reflux and cooled to below 2^0C to obtain a white crystalline wet solid. Obtained wet product was dried under vacuum at 50-55^0C for 1-2 h. Dry compound **ImpIX** was 3.6 g (71.42% yield based on **6**). Purity by HPLC: 99.27%. **FT-IR** (KBr, ν, cm^{-1}): 3053, 3016.1, 2960.8, 2938.0, 2822, 1669, 1614, 1585, 1536.9, 1462, 1448, 1415, 1380, 1313, 1273.3, 1221, 1177, 1123, 1077, 1034, 997, 985, 955, 884, 876, 853, 812, 795, 769, 643, 610, 569, 475; **^{1}H NMR** (400 MHz, DMSO-d_6): δ 2.03−2.10 (m, 6H), 2.12−2.18 (m, 2H), 2.56 (s, 3H), 2.58−2.60 (t, 2H), 3.02−3.09 (m, 3H), 3.91 (s, 3H), 4.1-4.19 (t, 2H), 6.91−6.93 (d, 1H), 7.10−7.16 (dd, 1H), 7.26−7.28 (m, 1H), 7.51−7.52 (d, 1H), 7.54−7.56 (m, 2H), 7.75−7.77 (d, 1H); **^{13}C NMR** (DMSO-d_6): 26.02, 26.40, 30.36, 34.34, 53.36, 54.90, 55.80, 67.16, 97.04, 97.31, 110.20, 111.02, 111.98, 112.23, 117.12, 122.36, 122.46, 123.06, 130.05, 130.11, 149.00, 152.66, 160.91, 162.60,165.09, 198.40; **MS** (ESI, m/z): 409.2 [M+H]+. **Anal.Calcd** (%) for $C_{24}H_{28}N_2O_4$ (408.49): C, 67.63; H, 6.91; N, 13.72% **Found** (%): C, 67.59; H, 6.87; N, 1370. HPLC retention time ~16.50 min.

RESULTS AND DISCUSSION

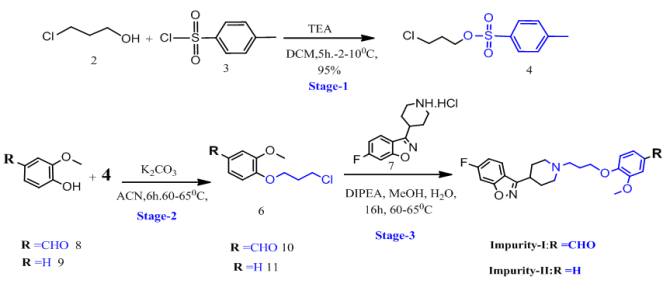
Synthetic procedure of Iloperidone **1** is well-known and they are commercially available in the literature[14-18]. Novel synthetic protocol (Scheme 1) starts with the quantitative synthesis of Iloperidone from a key intermediate, 1-[4-(3-chloro-propoxy)-3-methoxy-phenyl]-ethanone **6**. This altered method involves the change of key starting material from 1-bromo-3-chloropropane to toluene-4-sulfonic acid 3-chloro-propyl ester **4**. 3-chloropropan-1-ol **2** is treated with 4-methyl-

benzenesulfonylchloride **3** in presence of triethylamine as base and dichloromethane as solvent under optimized conditions to afford o-tosylated compound of toluene-4-sulfonic acid 3-chloro-propyl ester **4** This tosylated compound on condensation with 1-(4-hydroxy-3-methoxyphenyl) ethanone **5** in the presence of potassium carbonate in acetonitrile at ambient temperature gives 1-[4-(3-chloro-propoxy)-3-methoxy-phenyl]-ethanone **6** in good yield and 99% HPLC purity. The key feature of this reaction is reaction time reducedfrom 14-18 hours to 4-6 hours and formation of dimer impurity-10 is observed in little quantity which was the major drawback of the previously reported method. Finally, condensation of compound **6** with 6-fluoro-3-(4-piperidinyl)-1, 2-benzisoxazolehydrochloride **7**[14] in methanol using diisopropyl ethylamine as base resulted the desired Iloperidone **1** with good yields and chromatographic purity. The HPLC purity of compound **1** is 99.45% and the structure of compound **1** characterized by spectral analysis. The protonated molecular ion of Iloperidone**1** appeared at m/z 427.2 [M+H] + amu.



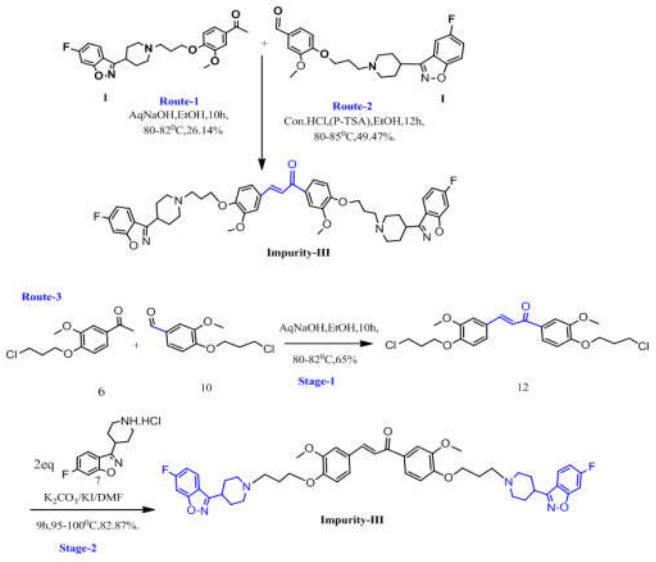
Scheme 1: Synthetic scheme of Iloperidone **1**

The impurity, Iloperidone related compound 1 **(Imp I)** formation is observed as metabolite of Iloperidone **1**. Iloperidone related compound 1 is also identified as an internal impurity in the synthesis of Iloperidone. Presence of 4-(3-chloro-propoxy)-3-methoxy-benzaldehyde **10** in the 1-[4-(3-chloro-propoxy)-3-methoxy-phenyl]-ethanone **6** as contaminant may cause the formation of close related substances **Imp I**. The possible formation of close related compound 1is demonstrated by synthesizing 4-(3-chloro-propoxy)-3-methoxy-benzaldehyde **10** from the condensation reaction of 4-hydroxy-3-methoxy benzaldehyde **8** and toluene-4-sulfonic acid 3-chloro-propyl ester **4** in the presence of potassium carbonate in acetonitrile at ambient temperature conditions in good yields 99% with HPLC purity. Compound **10** with 6-fluoro-3-(4-piperidinyl)-1, 2-benzisoxazole hydrochloride[14]**7** results the Iloperidone related compound 1 under similar experimental conditions with HPLC purity 99.42% which depicted in the Scheme 2.The protonated molecular ion peak of Iloperidone related compound 1 appeared at m/z 413.2 [M+H] + amu, IR spectrum of carbonyl group displayed C=O stretching frequency at 1652.2 cm^{-1} and ^{1}H NMR spectra indicates one aliphatic singlet proton absent at δ 2.56 ppm and one additional aromatic aldehyde proton at δ 9.87 ppm. ^{13}C NMR shows characteristic aldehyde carbonyl carbon signal at δ194.5 ppm. In addition, it is observed that no acetyl aliphatic carbon signals at δ 26.2 & 26.40 ppm. This Iloperidone related compound 1 was spiked with Iloperidone sample containing Iloperidone related compound 1 and confirmed related substance.



Scheme 2: Synthetic scheme of Iloperidone related compound 1 and 2 **(Imp I** and **Imp II)**

Iloperidone related compound 2 (**Imp II**) is identified as metabolite of iloperidone **1** and also as an impurity in the synthesis of iloperidone. Related compound 2 formation may occur due to contamination of 1-[4-(3-chloro-propoxy)-3-methoxy-phenyl]-ethanone **6** with 4-(3-chloro-propoxy)-3-methylbenzene **11**. Synthesis of related compound 2 from 4-(3-chloro-propoxy)-3-methoxy benzene **11** and 6-fluoro-3-(4-piperidinyl)-1, 2-benzisoxazole hydrochloride[14] **7** is achieved under similar experimental conditions with HPLC purity of 99.4% as shown in the S2. Compound **11** is prepared from 2-metoxy-phenol **9** and toluene-4-sulfonic acid 3-chloro-propyl ester **4** under same conditions with good yield and 99% HPLC purity. Iloperidone related compound 2 The protonated molecular ion of Iloperidone related compound 2 appeared at m/z 385.2 [M+H] + amu, IR spectrum not displayed C=O stretching frequency at 1652.2 cm^{-1} corresponding to carbonyl group and ^{1}H NMR indicates the absence of one aliphatic singlet proton at δ 2.56 ppm and one additional aromatic proton at δ 6.92 ppm which also supported by ^{13}C NMR. In^{13}C NMR signals related to keto carbonyl carbon and acetyl aliphatic carbon at δ198.58, 26.2 and 26.40 ppm respectively are not observed. In addition, quaternary carbon signals at δ164.1 & 164.3 ppm are also not found in ^{13}C NMR.



Scheme 3: Synthetic scheme of Iloperidone chalcone related dimer **impurity 2 Imp III**

Iloperidone chalcone related dimer impurity 2 (**Imp III**) is observed in major quantity around 11 % as an unknown impurity in iloperidone **1**.It is regarded as a potential degradation product during forced degradation studies using acid hydrolysis at higher temperature. This impurity may originate due to dimerization of Iloperidone related compound 1 in both acidic and base medium or condensation of

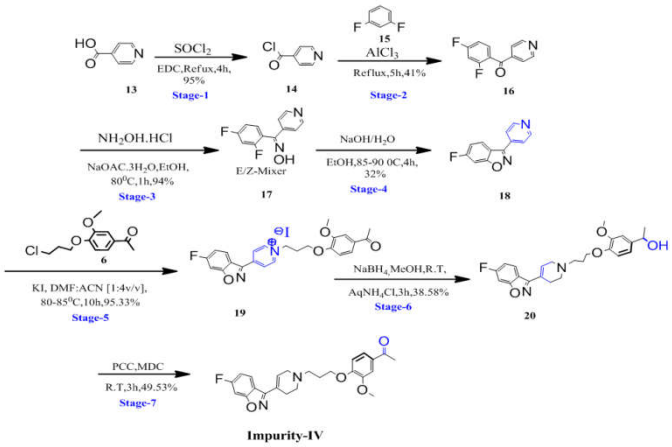
compound **6** and compound **10** followed by treatment with compound **7**. The synthetic protocol of chalcone related dimer **impurity III** is described in scheme 3.

As shown in Scheme 3, Iloperidone chalcone related dimer impurity 2 **Imp III** is synthesized by the dimerization reaction of Iloperidone **1** with iloperidone related compound 1 (**Imp I**) in ethanol and sodium hydroxide **(Route1**) or in ethanol and con HCl in presence of p-toluene sulfonic acid as catalyst (**Route 2**) at elevated temperature as yellow solid. The HPLC purity of Iloperidone chalcone related dimer compound 2 in both routes is 99.32% and 99.42% respectively. This impurity is also prepared by an alternative synthetic route (**Route 3**) from 1-[4-(3-chloro-propoxy)-3-methoxy-phenyl]-ethanone**6** and 1-[4-(3-chloro-propoxy)-3-methoxy-benzaldehyde **10** in ethanol and aqueous sodium hydroxide under reflux conditions to produce yellow precipitate of chalcone related compound of 1, 3-bis-[4-(3-chloro-propoxy)-3-methoxy-phenyl]-propenone **12** in good yields as shown in Scheme 3.The HPLC purity of compound **12** is 98.42%.In the final step, compound **12** and two equivalent ratio of compound **7**, [14] in presence of potassium carbonate and catalytically amount of potassium iodide in DMF under thermal conditions gives **impurity III**. The obtained crude product is recrystallized from methanol to get as yellow crystalline solid with good yields. The HPLC purity of **Imp III** is 99.38%. The structure of Iloperidone chalcone related dimer **impurity III** is confirmed by its spectral data.

The mass spectrum of **12** displayed the molecular ion peak at m/z 454.3 amu [$(M+H)^+$] and its fragment molecular ion peak at m/z 216.7 amu and m/z 227.3 amu, which confirms compound **10** moiety was attached at the C=C of chalcone. FTIR spectra of compound 12 shows peaks at 3079, 2932 cm^{-1} corresponding to stretching vibrations of aromatic -CH bands and =CH. The characteristic peaks of carbonyl functional group are observed with the strong bands at 1651 cm-1 and 1597 cm^{-1} which refers to carbonyl and carbon-carbon double bonds. The ^{1}H NMR spectrum of compound **12** displays the typical chalcone pattern of doublets of the alkene hydrogen at 7.69 and 7.85 ppm and that chalcone is trans isomer confirmed by large coupling constant 16Hz of the alkene hydrogen.^{13}C NMR spectrum of compound **12** shows the single carbonyl group signal at δ 189.59 ppm and multiple signals at δ 123.06 and 142.89 ppm due to doublets of the quaternary carbon respectively.

DehydroIloperidone analogue (**Imp IV**) is identified as an unknown impurity in synthesis of iloperidone **1**. It was observed to be a potential degradation product during the forced degradation studies at higher temperature. This is a potential impurity originated from manufacturing of 6-fluoro-3-(4-piperidinyl)-1, 2-benzisoxazole hydrochloride**7**[14]. Synthesis of 1-(4-{3-[4-(6-fluoro-benzo[d]isoxazol-3-yl)-3, 6-dihydro-2H-pyridin-1-yl]-propoxy}-3-methoxy-phenyl)-ethanone (**Imp IV**) is reported in the literature from 6-fluoro-3-pyridin-4-yl-benzo[d] isoxazole[14, 16, 18].

The synthetic protocol (Scheme 4) starts from isonicotinic acid **13** which treated with thionyl chloride to provide isonicotinyl chloride **14**. Compound **14** undergoes Friedal craft acylation with 1, 3-difloro benzene in the presence of $AlCl_3$ to give compound **16**. This keto compound is converted to oxime in the presence of hydroxyl amine hydro chloride and subjected for cyclization in basic medium to get compound **18**. 6-fluoro-3-pyridin-4-yl-benzo[d]isoxazole **18** afford quaternion iodide compound **19** through condensation reaction with 1-[4-(3-chloro-propoxy)-3-methoxy-phenyl]-ethanone **6** in presence of potassium iodide, N, N-dimethyl form amide and acetonitrile at higher temperature.



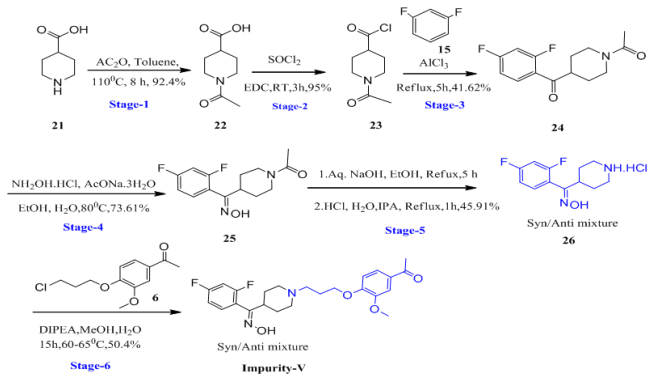
Scheme 4 Synthetic scheme of DehydroIloperidone analogue (**Imp IV**)

The compound **19** having pyridinium iodide ring reduced with sodium borohydride to form secondary alcohol compound **20**. Thus, the compound **20** on oxidation with pyridinium chloro-chromate in DCM at room temperature yields crude compound **Imp IV**. This crude compound is purified by column chromatography to obtain dehydroiloperidone analogue **Imp IV** as white powder. The HPLC purity of DehydroIloperidone analogue **Imp-IV** is 99.48%. The protonated molecular ion of DehydroIloperidone analogue **Imp IV** appeared at m/z 425.2 [M+H] + amu. FTIR spectrum displayed carbonyl group C=O stretching frequency at 1732.2 cm^{-1} and 1666 cm^{-1}.^{1}H NMR shows the absence of three aliphatic protons in the δ 2.13-2.18 ppm range and presence of one signal at δ 6.89 ppm corresponds to additional aromatic sat, H-C=C Pyrid proton.^{13}C NMR also confirms the characteristic carbonyl carbon signal at δ196.66 ppm. In addition to this, it is observed aliphatic H-C=C-C Pyrid carbon signals at δ 126.8 and δ129.60 ppm respectively. The intermediates of this synthetic procedure are confirmed by spectral data.

Iloperidone process related compound 3 (**Imp V**) is also identified as metabolite of Iloperidone **1** and as an impurity in Iloperidone synthesis. This potential impurity **V** may originate from manufacturing of 6-fluoro-3-(4-piperidinyl)-1, 2-benzisoxazole hydrochloride **7**. Iloperidone process related compound 3 **V** is prepared from 1 (2, 4-difluoro-phenyl)-piperidin-4-yl-methanone oxime hydrochloride **26**. Mixture of Syn and anti-isomers of compound **26** are condensed with 1-[4-(3-chloro-propoxy)-3-methoxy-phenyl]-ethanone**6** in Diisopropyl ethylamine as base in methanol solvent to give Iloperidone process related compound 3 (**ImpV**) described in Scheme 5.

This synthetic method starts from treatment of piperidine-4-carboxylic acid **21** with acetic anhydride in toluene under reflux conditions to give 1-acetyl-piperdine-4-caroxylicacid **22**. Compound **22** reacts with thionyl chloride gives acid chloride derivative **23**. This derivative undergoes Friedal crafts acylation with 1, 3-difloro benzene in the presence of $AlCl_3$ in EDC to afford compound **24**. The keto group of compound **24** is converted to oxime by treating with hydroxyl amine hydrochloride to have compound **25**. De-protection of N-acetyl group of compound **25** in acidic conditions results 1 (2,

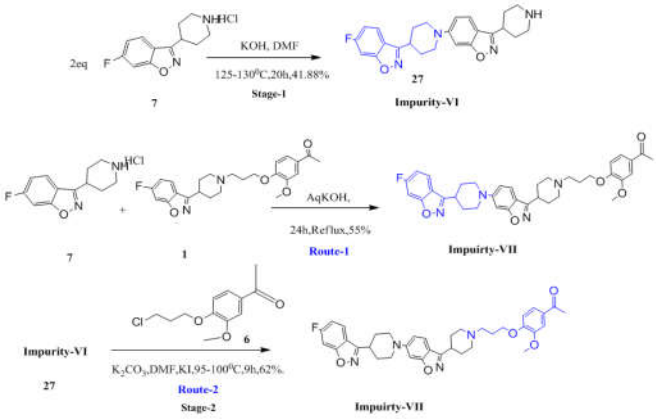
4-difluoro-phenyl)-piperidin-4-yl-methanoneoxime hydrochloride **26**. All the intermediates are characterized by spectral analysis.



Scheme 5 Synthetic scheme of Iloperidone process related compound 3 (**Imp V**)

The HPLC purity of Iloperidone process related compound 3 (**Imp V**) is 98.99%. The protonated molecular ion of Iloperidone process related compound 3 (V) appeared at m/z 447.2 $[M+H]^+$ amu and its sodium adduct at m/z 469.2 amu $[(M+H+Na)^+]$. IR spectrum confirms the presence of oxime (=NOH) group by showing C=N frequency at 1672.2 cm^{-1}, OH stretching frequency at 3441 cm^{-1} and C-F stretching frequency at 1154.2 cm^{-1}.One additional aromatic singlet broad proton at δ 10.2 ppm (Syn and Anti oxime of OH) is observed in ^{1}H NMR, aromatic quaternary carbon signal at δ 165.6 ppm in ^{13}C NMR.

Iloperidone process related dimer impurity14 (**Imp VI**) is observed as an impurity in synthesis of Iloperidone **1**. Process related dimer impurity **VI** results due to self-condensation of trace amount ofcompound **7** present in Iloperidone **1**. The condensation reaction of compound **7** is mediated by potassium carbonate, KOH in N, N-dimethyl form amide at thermal conditions (s Scheme-6). The HPLC purity of Iloperidone process related dimer impurity14 **VI** is 99.35% and its structure is confirmed by spectral analysis. The Mass spectrum shows molecular ion peak at m/z 421.1[M+H]+.This Iloperidone process related dimer impurity-14 **VI** was spiked with Iloperidone sample containing Iloperidone process related dimer impurity-14 **Imp VI** and confirmed related substance.

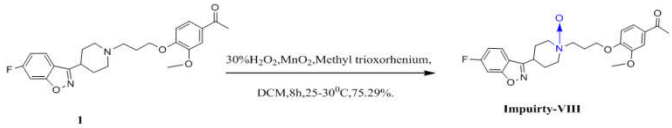


Scheme 6: Synthetic scheme of Iloperidone process related dimer impurity 14 and 9 (**Imp VI** and **Imp VII**)

As shown in the Scheme 6, iloperidone dimer impurity 9 (**Imp VII**) can be synthesized in two methods. This compound **ImpVII** is regarded as potential impurity Iloperidone which forms during process development of Iloperidone. After thorough investigation on this impurity, we have demonstrated the formation of dimer impurity 9 in two synthetic routes. The first route describes the reaction between traces of **VI** in **7** and compound **6** leads to give impurity **VII** (sScheme 6). The second alternate route, it is presumed that the Iloperidone **1** formed in the reaction might be reacted with compound **7** to provide impurity **Imp VII**.

The Imp**VII** is synthesized from condensation of [3-(6-fluoro-benzo[d]isoxazol-3-yl)-propyl] -(3-piperidin-4-yl-benzo[d]isoxazol-6-yl)-amine **27** (**Imp VI**) (1eq.) and 1-[4-(3-chloro-propoxy)-3-methoxy-phenyl]-ethanone **6** (1eq.) in presence of potassium carbonate and catalytic amount of potassium iodide in N,N-dimethyl form amide at ambient temperature with HPLC purity 99.51%. In another method 6-fluoro-3-(4-piperidinyl)-1, 2-benzisoxazole hydrochloride **7** (1eq.) condensed with iloperidone **1** (1eq.) in presence of potassium hydroxide in water at ambient temperature yields related substance 14 **Imp VII** with HPLC purity 99.41%. The structure of related substance **Imp VII** is confirmed by spectral analysis. Mass spectrum showed mass peak at m/z 627.2 $[M+H]^+$.

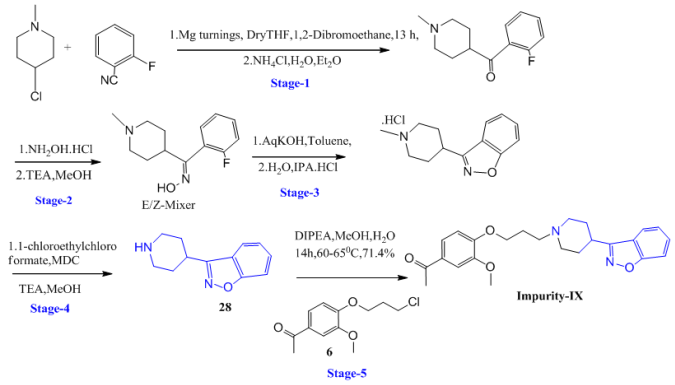
Iloperidone related impurity11(**Imp VIII**) is identified as Iloperidone N-oxide, which is present in the product **1** in low amount and it regarded as a potential degradation product during forced degradation studies using hydrogen peroxide. The synthesis of impurity **VIII** can be achieved by treating 1-(4-(3-(4-(6-fluorobenzo[d] isoxazol-3-yl) piperidin-1-yl) propoxy)-3-methoxyphenyl) ethanone **1** with catalytic amount of MnO_2 and methyl trioxorhenium by using hydrogen peroxide (30 %) in methylene dichloride at ambient conditions. It is N-oxidation of Iloperidone **Imp-VIII,** which is further purified by crystallization in isopropyl alcohol with good purity 99.32 % by HPLC and yield is 75.29% (Scheme 7). The structure of impurity **VIII** is confirmed by spectral analysis. Mass spectrum showed mass at m/z 443 $[M+H]^+$.This Iloperidone N-oxide impurity11 (**Imp VIII**) was spiked with Iloperidone sample containing Iloperidone N-oxide impurity-11(**Imp VIII**) and confirmed as related substance.



Scheme 7 Synthetic scheme of Iloperidone N-oxide impurity 11 (**Imp VIII**)

Desflouro iloperidone impurity 8 (**Imp IX**) is observed as an impurity during the synthesis of Iloperidone **1**. Contamination of 6-fluoro-3-(4-piperidinyl)-1, 2-benzisoxazole hydrochloride **7** with Desflouro isoxazole intermediate **28** leads to this related substance 8 (**Imp IX**). Removal of impurity **IX** in iloperidone **1** is very difficult due to structural similarity with **1**. Related substance **IX** is prepared alone from compound **28**, which is prepared by reported method from the literature method[19]. Desflouro iloperidone impurity 8 **Imp IX** is synthesized from the condensation reaction between compound **28** and compound **6** in Diisopropyl ethylamine as base in methanol (Scheme 8) with HPLC purity of 99.27%. The protonated molecular ion of Desflouroiloperidone impurity 8 **Imp IX** appeared at m/z 409.2 [M+H] + amu. C-F stretching frequency at 1143.2 cm^{-1} is absent in IR spectrum.^{1}H NMR and ^{13}C NMR spectra indicates one additional aromatic proton at δ 7.54, and aromatic carbon signals at δ 130.11 ppm and absent of quaternary carbon signals at 163.53 and 163.61 ppm. This Desflouro iloperidone impurity 8 (**Imp IX**) was spiked with

Iloperidone sample containing Desflouro iloperidone impurity 8 **(Imp IX)** and confirmed related substance.



Scheme 8 Synthetic scheme of Desflouro Iloperidone analogue impurity 8 **(Imp IX)**

Iloperidone related impurity substances **I** and **II** may originate from the key starting material of acetovanillone which can be controlled by raw material specification of acetovanillone. The traces of these impurities can be removed during isolation of iloperidone. Iloperidone related substances **III**, **V** and **VIII** are removed from the iloperidone by recrystallization in methanol. Iloperidone related substances **VI**, **VII** and **IX** are process related impurities. These impurities can be controlled by carrying the reaction using lower volume of solvent, different bases, mole ratio, reaction time and temperature. Further, these impurities can also be removed from iloperidone by additional purification in isopropanol.

CONCLUSION

In view of regulatory importance of the impurities in the API, a detailed investigation on various impurities in iloperidone is conducted. Different process related substances, metabolite, degradation impurities are identified. The identified impurities (**I-IX**) are synthesized and characterized using various spectroscopic techniques like ^{1}HNMR, ^{13}CNMR and infrared (FTIR) spectrometry. These characterization prospects are well supported by liquid chromatography-mass spectrometry (LC-MS) data. These Products are very much useful for toxicological studies, validation studies and have regulatory significance. Thus, we have described an efficient, industrial scale novel synthetic approach for synthesis of iloperidone **1**. The key feature of this protocol is the change of key starting material from 1-bromo-3-chloropropane to toluene-4-sulfonic acid 3-chloro-propyl ester **4** which facilitates the preparation of intermediate of interest 4-(3-chloropropoxy)-3-methoxyacetophenone **6** in DMF and condensation of this intermediate **6** with 6-fluoro-3-(4-piperidinyl)-1, 2-benzisoxazolehydrochloride **7** to gives the Iloperidone **1** in presence of DIPEA base and aqueous methanol under optimized conditions with good yields and chromatographic purity process to meet ICH requirements instead of K_2CO_3 base and DMF as a solvent at elevated temperature condition's procedures.

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Conflicts of Interest

There are no conflicts to declare

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