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SYNTHESIS AND CHARACTERIZATION OF POTENTIAL IMPURITIES OF ARIPIPRAZOLE

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ABSTRACT: Aripiprazole is an anti-psychotic drug used in the treatment of psychosis, including schizophrenia, and during process development for Aripiprazole, we observed two related substances. This paper describes the preparation, identification and proposed structures of the impurities 7-(4-(4-(2-chlorophenyl) piperazine-1-yl) butoxy) - 3, 4 – dihydroquinoline - 2(1H) - one and 7- (4-(4-(3-chlorophenyl)piperazin-1-yl) butoxy)-3,4-dihydroquinoline-2(1H)-one formed during reaction of 7-(4-bromobutoxy)-3, 4-dihydroquinoline-2(1H)-one with 1-(2, 3-dichloro phenyl) Piperazine Hydrochloride to form Aripiprazole.

INTRODUCTION: Aripiprazole knew as 7-(4-(4-(2, 3-Dichlorophenyl)piperazin-1-yl) butoxy)-3, 4-dihydroquinoline-2(1*H*)-one is an anti-psychotic drug [1, 2] used in the treatment of psychosis including schizophrenia [3]. Aripiprazole developed by Otsuka Pharmaceutical Co. Ltd. Schizophrenia is the most common type of psychosis caused by an excessive neurotransmission activity of the dopaminergic nervous system in the CNS. Aripiprazole, a carbostyril derivative, functions as a partial agonist [4-7] at the dopamine D_2 and serotonin 5 HT_{1A} receptors and as an antagonist at serotonin 5-HT_{2A} receptor. It is a novel antipsychotic agent who is an agonist of dopamine (DA) autoreceptors and an antagonist of postsynaptic DA receptors.

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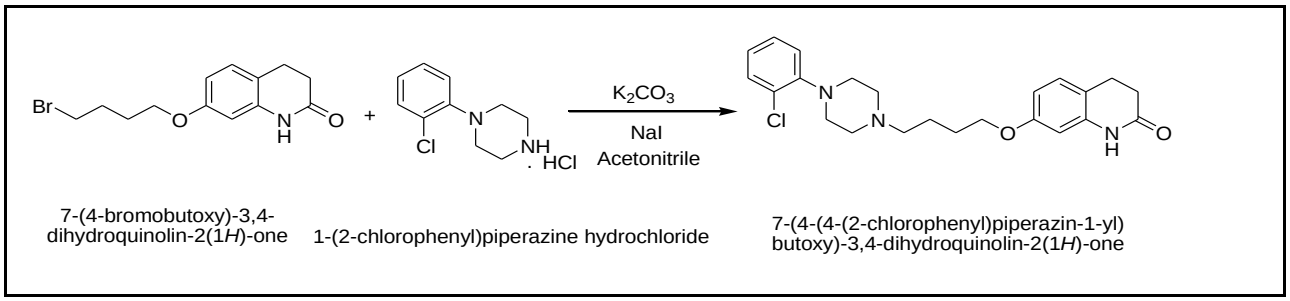
Aripiprazole is known to be effective towards reducing the positive symptoms of schizophrenia with fewer side effects as compared to the psychotic drugs known in the literature. Aripiprazole-induced catalepsy is at 10 times higher dose than that required for the antagonism of APO-induced stereotypy (ED_{50} value of 7.8 mol/kg po). Aripiprazole showed lower potential to induce catalepsy than the standard agent and did not show α1-adrenoreceptor antagonist activity. In addition to the dual activities, Aripiprazole reversed the reserpine-induced increase in tyrosine hydroxylase activity in mouse and rat brain. Aripiprazole was also approved for acute manic and mixed episodes associated with bipolar disorder; as an adjunct for major depressive disorder [8] and to treat irritability in children with autism [9].

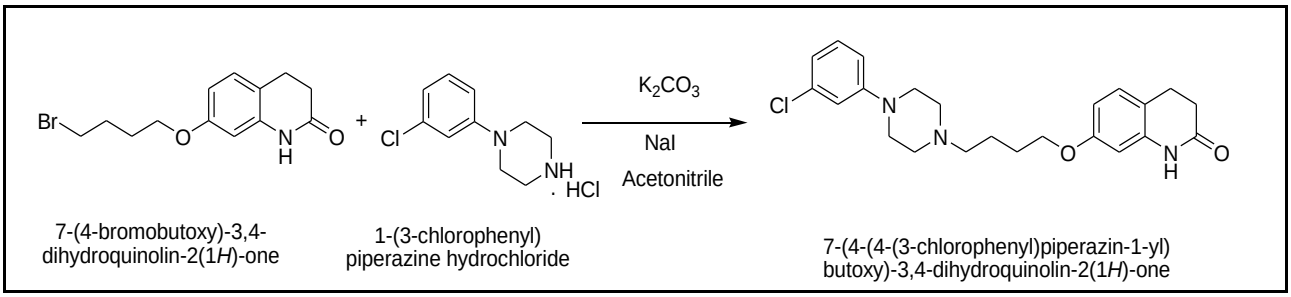
The presence of impurities in active pharmaceuticals ingredients (API) can impact the quality and safety of drug products. International Conference on Harmonization (ICH) guidelines recommend identifying and characterizing all

impurities present in an API at a level of < 0.15% [10]. This limit is calculated on the bases of daily dosage. However, in Aripiprazole, the limit is further tightening to 0.1%. These impurities are required in pure form to check the analytical performance characteristic such as specificity, linearity, range, accuracy and precision, the limit of detection (LOD), limit of quantification (LOQ), robustness, system suitability testing, and relative retention factor [11].

A number of impurities is possible in final Aripiprazole, some of which are starting material (like 7-hydroxy-3, 4-dihydroquinoline-2(1H)-one and 1 - (2, 3-dichloro phenyl) piperazine hydrochloride. Other impurities like Aripiprazole-1-N-oxide, 7-[4-{4-(2,3-dichlorophenyl)-1-piprazinyl} butoxy] - 3, 4-dehydro-2-(1H)-quinolinone are also reported in literature [12]. 1-(2, 3-dichloro phenyl) piperazine hydrochloride is our key starting material for the synthesis of Aripiprazole. In this, there is the possibility of the presence of 1-(2-chloro phenyl) piperazine hydrochloride and 1-(3-chloro phenyl) piperazine hydrochloride as impurities, although their limit is NMT 0.1%.

These also react with 7-(4-bromobutoxy)-3, 4-dihydroquinoline-2(1H)-one in same fashion as 1-(2, 3-dichloro phenyl) piperazine hydrochloride and form impurities 7-[4-{4-(2-chlorophenyl)- piprazin-1-yl}butoxy]-3, 4-dihydroquinolin-2(1H)-one and 7-[4-{4-(3-chlorophenyl)-piprazin-1-yl}butoxy]-3, 4-dihydroquinolin-2(1H)-one as shown below:





In our current work, we identified these two related substances in Aripiprazole API. Their detection, origin, synthesis, and characterization are described in this article.

EXPERIMENTAL: Solvents and reagents were obtained from commercial sources and used without purifications. The IR spectra (ν max cm^{-1}) were recorded in solid state KBr dispersion using an FTIR (Shimadzu FTIR Prestige 21 Spectrophotometer operating range 400-4000 cm^{-1} with a resolution of 5 cm^{-1}). The ^{1}H NMR and ^{13}C NMR spectra recorded on a Bruker AB-400 instrument frequency 400 MHz instrument and Bruker 400 MHz instrument. The mass spectra were recorded on a Thermo Scientific LCQFLEET ion trapped instrument. We have synthesized all these compounds as described in this experimental section.

Preparation of 7- (4-(4-(2-chlorophenyl)-piperazine-1-yl) butoxy)-3, 4-dihydroquinoline-2(1H)-one: A mixture of Acetonitrile (100mL), 7-(4-bromobutoxy)-3, 4-dihydroquinoline-2(1H)-one (10 g), Potassium Carbonate (13.5 g), 1-(2-chloro phenyl) piperazine hydrochloride (9.0 g) and sodium iodide (1 g) heated to 80°C. Reaction mass maintained at this temperature for 3-4 h. After completion of the reaction, mass is cooled to 50-55 °C. Maintain at this temperature for a further 30 min. The reaction mass is filtered to remove insoluble, if any. Clear filtrate, cool to 25-30°C.

Product is precipitated and stirs the mass for 30 minute. Filter and dry to get pure 7-(4-(4-(2-chlorophenyl) piperazin-1-yl) butoxy) - 3, 4-dihydroquinoline-2(1H)-one.

Weight: 9.0 g (Yield: 64.8 %); HPLC purity: 99.46%

Off White Solid, Melting Point: 100-107°C; IR (KBr) ν_{max} (cm^{-1}) 1678 (-C=O), 1232 1037.7 (-C-O-C), 1182.36 (C-N), 1141.8 (C-Cl), 2951, 2823 (Aliphatic C-H); Mass (%): M+ 414.24 (100); ^{1}H NMR (MeOD): δ 1.57 (4 H Aliphatic.), 2.43 (2 H Aliphatic. near to N, 2 H quinolinone), 2.54 (4 H of piperazine), 2.73 (2 H quinolinone), 3.2 (4 H of piperazine), 3.96 (2 H Aliphatic near to N), 6.34, 7.24 (H Aromatic); ^{13}C NMR (MeOD): δ 24.16, 25.43, 68.82, 54.44 (Aliphatic C), 174.01 (amide C), 28.43, 31.96 (quinolinone C), 103.29,160.05 (aromatic C), 48.4,54.4 (piperazine C).

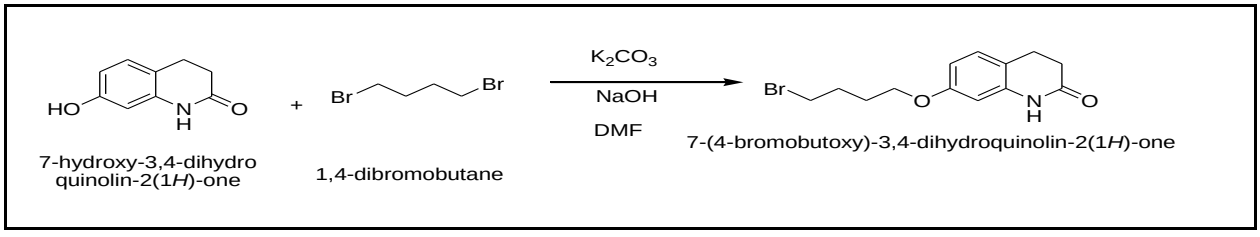
Preparation of 7 - (4-(4-(3-chlorophenyl)-piperazin-1-yl) butoxy) - 3, 4-dihydroquinoline-2(1H)-one: A mixture of Acetonitrile (100 mL), 7-(4-bromobutoxy)-3, 4-dihydroquinoline-2(1H)-one (10 g), Potassium Carbonate (13.5 g), 1-(2-chloro phenyl) piperazine hydrochloride (9.0 g) and Sodium Iodide (1 g) heated to 80°C. Reaction mass maintained at this temperature for 3-4 h. After completion of the reaction, mass is cooled to 50-55 °C. Maintain at this temperature for a further 30 minutes. The reaction mass is filtered to remove insoluble if any. To the clear filtrate add 150 mL water at room temperature. Product is precipitated and stirs the mass for 30 min. Filter and dry to get 7-(4-(4-(2-chlorophenyl) piperazine-1-yl) butoxy) - 3, 4-dihydroquinoline-2(1H)-one. Product is further recrystallized in ethanol to get the pure compound.

Weight: 8.0 g (Yield: 57.6%); HPLC purity: 98.70%

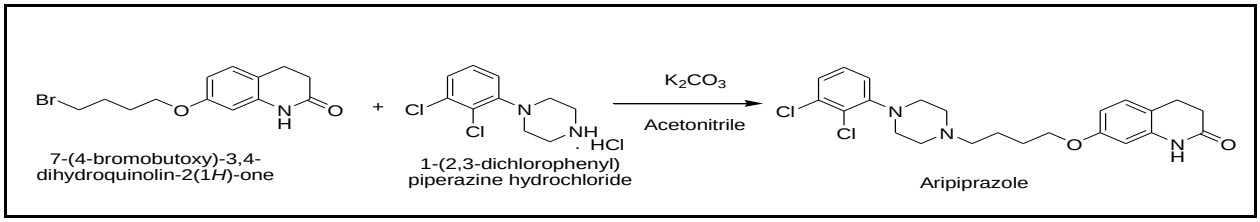
Off White Solid, Melting Point: 97-99°C. IR (KBr) ν_{max} (cm^{-1}) 1678 (-C=O), 1232 1028 (-C-O-C), 1176.58 (C-N), 1151 (C-Cl), 2941, 2819 (Aliphatic C-H); Mass (%): M+ 414.21(100); ^{1}H NMR (MeOD): δ 1.57 (4 H Aliphatic), 2.42 (2 H Aliphatic near to N, 2 H quinolinone), 2.49 (4 H of piperazine), 2.72 (2 H quinolinone), 3.2 (4 H of piperazine), 3.94 (2 H Aliphatic near to N), 6.34, 7.07 (H Aromatic); ^{13}C NMR (MeOD): δ 24.17, 25.43, 69.82, 59.35 (Aliphatic C), 174.07 (amide C), 28.40, 31.97 (quinolinone C), 103.30,160.03 (aromatic C), 48.4,54.1 (piperazine C).

RESULTS AND DISCUSSION: Aripiprazole was synthesized by the known literature synthetic procedure.[1] One key starting material, 7-hydroxy-3, 4-dihydroquinoline-2(1H)-one was reacted with 1,4-dibromobutane in Dimethyl formamide and Potassium Carbonate and quench in water to form 7-(4-bromobutoxy)-3,4-dihydroquinoline-2(1H)-one. 7-(4-bromobutoxy)-3, 4-dihydroquinoline-2(1H)-one is reacted with second key starting material 1-(2, 3-dichloro phenyl) piperazine hydrochloride in the presence of Acetonitrile and Potassium Carbonate to form Aripiprazole **Scheme 1**.

Stage 1: Preparation of 7-(4-bromobutoxy)-3, 4-dihydroquinoline-2(1H)-one

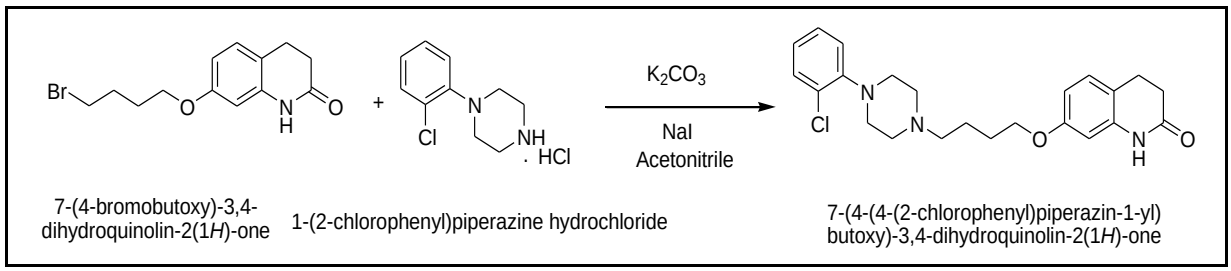


Stage 2: Preparation of Aripiprazole



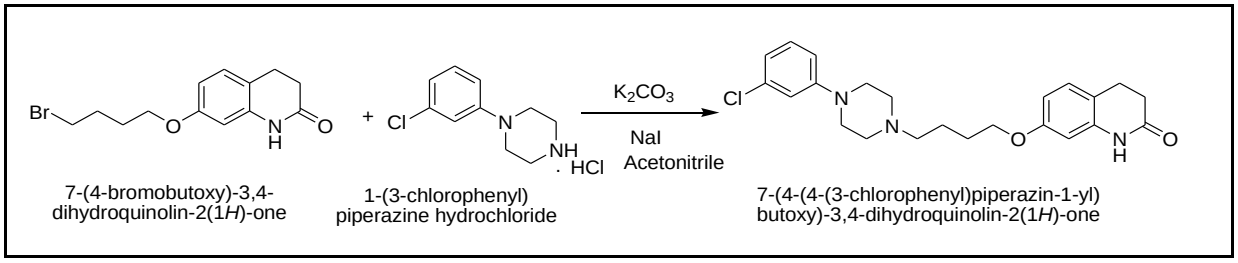
SCHEME 1: ROUTE OF SYNTHESIS OF ARIPIPRAZOLE

This second key starting material 1-(2, 3-dichloro phenyl) piperazine hydrochloride may contain 1-(2-chlorophenyl) piperazine hydrochloride and 1-(3-chlorophenyl) piperazine hydrochloride as impurities. 1 - (2-chlorophenyl) piperazine hydrochloride present in second key starting material as an impurity also react with 7- (4-bromobutoxy) - 3, 4-dihydroquinoline-2(1H)-one in presence of Acetonitrile and Potassium Carbonate to form impurity 7 - (4-(4-(2-chlorophenyl) piperazine-1-yl) butoxy) – 3, 4-dihydroquinoline-2(1H)-one **Scheme 2**.



SCHEME 2: Synthetic scheme of 7-(4-(4-(2-chlorophenyl) piperazine-1-yl) butoxy)-3, 4-dihydroquinoline-2(1H)-one

The mass spectra of 7-(4-(4-(2-chlorophenyl) piperazine-1-yl) butoxy) -3, 4 - dihydroquinoline-2(1H)-one showed the molecular ion peak at m/z 414.21. The IR spectrum (cm^{-1}) displayed (-C-O-C) in 1232 and (C-Cl) displayed in 1151. 1-(3-chloro phenyl) piperazine hydrochloride present in second key starting material as an impurity. Also react with 7 - (4-bromobutoxy)-3, 4-dihydroquinoline-2(1H) - one in presence of Acetonitrile and Potassium Carbonate to form impurity 7-(4-(4-(3-chlorophenyl) piperazin-1-yl) butoxy)-3,4-dihydro-quinolin-2(1H)-one **Scheme 3**.



SCHEME 3: Synthetic scheme of 7-(4-(4-(3-chlorophenyl) piperazine-1-yl) butoxy)-3, 4-dihydroquinoline-2(1H)-one

The mass spectra of 7-(4-(4-(3-chlorophenyl) piperazin-1-yl) butoxy) - 3, 4-dihydroquinolin-2(1H)-one showed the molecular ion peak at m/z 414.24. The IR spectrum (cm^{-1}) displayed (-C-O-C) at 1176.58 and (C-Cl) displayed at 1151. Both the impurities 7-(4-(4-(2-chlorophenyl) piperazin-1-yl) butoxy) -3, 4-dihydroquinolin-2(1H)-one and 7-(4-(4-(3-chlorophenyl) piperazin-1-yl) butoxy) -3, 4-dihydroquinolin-2(1H)-one are well controlled below 0.1 % after final purification.

CONCLUSION: To have a thorough understanding of the formation of impurities during the manufacturing of Aripiprazole, it is essential to have detailed information about the impurities, their origin, and synthetic route. Given regulatory importance of the impurities in API, a detailed study on these impurities, which are novel, in Aripiprazole was studied, and these impurities were synthesized and controlled well within a limit ≤ 0.10%. They were characterized using various spectroscopic techniques such as Mass, ^{1}H NMR, ^{13}C NMR, and IR.

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CONFLICT OF INTEREST: Nil

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