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Original Article

Synthesis, characterization and identification of sertraline hydrochloride related impurities

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ABSTRACT

Sertraline hydrochloride is an antidepressant of the selective serotonin reuptake inhibitor (SSRI) class, is synthesized for commercial use as a drug substance in highly pure form. During commercial production of Sertraline Hydrochloride, two unknown impurities were detected in final API at levels ranging from 0.05% to 0.15% in gas chromatography (GC) analysis. For regulatory compliances, it was mandatory to identify these two unknown impurities. In present work these two impurities are identified, synthesized and characterized as 1-(3,4-Dichlorophenyl)-1,2,3,4-tetrahydronaphthalene and 1-(3,4-Dichlorophenyl)-1,2-dihydronaphthalene.

Keywords: Sertraline, Sertraline hydrochloride.

INTRODUCTION

Setraline is chemically known as (1*S*,4*S*)-4-(3,4-dichlorophenyl)-*N*-methyl-1,2,3,4-tetrahydro naphthalen-1-amine. Setraline, having a molecular weight of 306.229 and its molecular formula is $C_{17}H_{17}Cl_2N$. Sertraline (trade names Zoloft and others) is an antidepressant of the selective serotonin reuptake inhibitor (SSRI) class [1, 2]. It was introduced to the market by Pfizer in 1991. Sertraline is primarily prescribed for major depressive disorder in adult outpatients as well as obsessive-compulsive disorder, panic disorder, and social anxiety disorder, in both adults and children [3, 4, 5]. In 2013, it was the most prescribed antidepressant and second most prescribed psychiatric medication on the U.S. retail market, with over 41 million prescriptions [6].

Sertraline hydrochloride drug substance is official in United State pharmacopoeia (USP) [7] as well as European Pharmacopoeia (EP) [8]. The listed organic impurities and method of analysis by gas chromatography is same in both pharmacopoeias. In almost all commercial batches, two unknown impurities are observed at relative retention time (RRT) = 0.65 and (RRT) = 0.69 ranging about 0.05% to 0.15%. Here in this research article, attempts were made successfully to identify, synthesize and characterise these two unknown impurities as 1-(3,4-Dichlorophenyl)-1,2,3,4-tetrahydronaphthalene at relative retention time (RRT) = 0.65 and 1-(3,4-Dichlorophenyl)-1,2-dihydronaphthalene at relative retention time (RRT) = 0.69. These impurities further can be used as reference standards for corresponding gas chromatography (GC) analysis of Sertraline hydrochloride.

MATERIAL AND METHODS

The progress of reaction was monitored on TLC using hexane: ethyl acetate (9:1) as eluent system. IR spectra were recorded on Shimadzu FTIR 8400 spectrophotometer. ^{1}H-NMR spectra and ^{13}C-NMR spectra were recorded on Bruker spectrometer 400MHz (chemical shifts, δ, in ppm). The solvents for NMR spectra were deuterochloroform ($CDCl_3$) and deuterodimethylsufloxide (DMSO-d6) unless otherwise stated. GCMS spectra were recorded on a GCMSD_ALS at an iononizing voltage of 70eV. All the chemicals used were of analytical grade.

A] Synthesis of Sertraline Unknown Impurity at RRT=0.65 i.e. 1-(3,4-Dichlorophenyl)-1,2,3,4-tetrahydronaphthalene(2)

In an autoclave, take sertralone (1) (20 gm, 0.0687) with 5% Pd-C catalyst (1.0 gm) in methanol (300 ml) under nitrogen atmosphere. Carry out hydrogenation using hydrogen gas pressure at 2.0 kgf with temperature of the reaction mass 30-35^{0}C. Maintain at same temperature and pressure for

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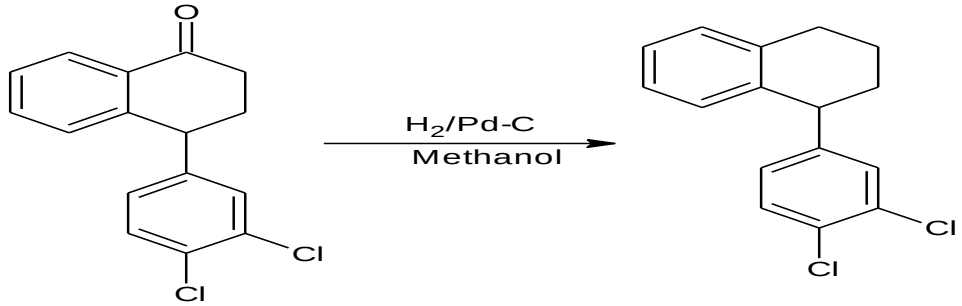
complete conversion monitored on TLC. After reaction completion, release the hydrogen completely and filter the reaction mass through hyflow bed under nitrogen blanketing. Wash the catalyst bed with methanol (25 ml x 2 times). Collect all filtrate and washing of methanol and distill out methanol completely. After complete removal of methanol, add hexane (100 ml) to the reaction mass at 30-35^{0}C. Filter the insoluble material through hyflow (10 gm). Wash it with hexane (25 ml). Collect hexane layer and then add silica (20 gm) to the reaction mass. Stir for half an hour at 30 to 35^{0}C so that colour impurity adsorbed on silica. Filter the silica and wash it with hexane (25ml). Collect hexane filtrate and distill out hexane completely to get oil as product, which is characterised by GCMS, 1H-NMR, 13C-NMR techniques and identified as 1-(3,4-Dichlorophenyl)-1,2,3,4-tetrahydronaphthalene (2).
Yield- 15.0gm, 78.78%; Purity-98.7%;

GCMS_ALS: 276.0 [M-H] at RT=24.770;
^{1}H-NMR: (400MHz, $CDCl_3$): δ1.8322-δ2.2374 (m, 4H, -CH_2-), δ2.8460-δ2.9978 (m, 2H, -CH_2-), δ4.1154- δ4.1476 (t, 1H, >CH-), δ6.8388- δ7.3882 (m, 7H, Aromatic);
^{13}C-NMR: (400MHz, $CDCl_3$): δ20.63, δ29.49, δ32.99, δ44.73, δ125.79, δ126.27, δ128.14, δ130.56, δ132.10, δ137.37, δ137.82, δ147.77.

Reaction Scheme:



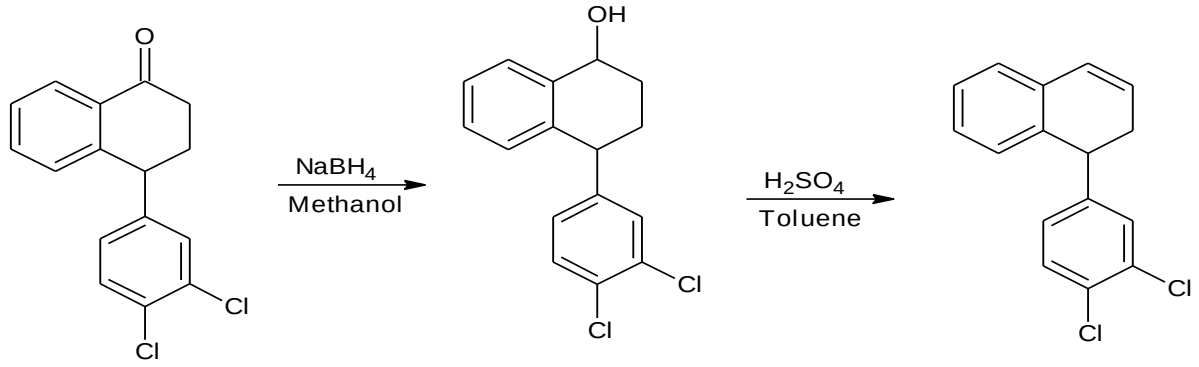
Sertralone (1) 1-(3,4-Dichlorophenyl)-1,2,3,4-Tetrahydronaphthalene (2)

B] Synthesis of Sertraline Unknown Impurity at relative retention time (RRT) = 0.69 i.e. 1-(3,4-Dichlorophenyl)-1,2-dihydronaphthalene (4)

Take Sertralone (1) (50 gm, 0.1718) in methanol (150 ml) and apply chilling to chill the reaction mass to 10-15^{0}C. Add sodium borohydride (5.0 gm, 0.132) by maintaining temperature of the reaction mass to 10-15^{0}C. Maintain the reaction mass at 10-15^{0}C for complete conversion monitored on TLC. After reaction completion, distill out methanol completely under vacuum at 40-450C and add water (100 ml) and methylene dichloride (MDC) (100 ml) to the reaction mass. Separate the MDC layer and distill out MDC completely to get brown colour liquid product Sertralon-1-ol (3). Take this intermediate product sertralon-1-ol (3) in toluene (235 ml) and add few drops of concentrated sulphuric acid (1.0 ml). Apply heating to raise the temperature of the reaction mass to reflux so that corresponding water is removed from the reaction mass and reaction carry forward to get complete conversion monitored on TLC. After complete removal of water, cool the reaction mass to 30-35^{0}C and wash toluene layer with water (100 ml x 2 times). Collect toluene layer and distill out toluene completely at 90-100^{0}C under vacuum to get oily product. Add hexane (235 ml) to the reaction mass and filter it over hyflow under vacuum. Collect hexane layer and distill out hexane completely under vacuum at 30-40^{0}C to get white colour solid product, which is characterised by GCMS, 1H-NMR, 13C-NMR techniques and identified as 1-(3,4-Dichlorophenyl)-1,2,3,4-tetrahydronaphthalene (4).
Yield- 36.0gm, 76.19%; Purity-99.36%;

GCMS_ALS: 274.0 [M-H] at RT=17.278;
^{1}H-NMR: (400MHz, $CDCl_3$): δ2.5555-δ2.7850 (m, 2H, -CH_2-), δ4.1205-δ4.1610 (t, 1H, >CH-), δ5.9939-δ6.0398 (m, 1H, =CH-), δ6.5968-δ6.6209 (d, 1H, =CH-), δ6.8823-δ7.4141 (m, 7H, Aromatic);
^{13}C-NMR: (400MHz, $CDCl_3$): δ31.63, δ42.80, δ126.37, δ130.29, δ132.25, δ133.82, δ136.34, δ144.86.

Reaction Scheme:



Sertralone (1) Sertralon-1-ol (3) 1-(3,4-dichlorophenyl)-1,2-dihydronaphthalene (4)

RESULTS AND DISCUSSION

Sertraline hydrochloride is a very widely used drug as Antidepressant worldwide. During its GC analysis as per pharmacopeia methods, we observed that two unknown impurities at RRT=0.65 and RRT=0.69 were present in all commercial batches. Due to regulatory constraint, it was mandatory to identify these two impurities.

First we developed a method to separate out these two unknown impurities and carried out GCMS analysis by which we identified the molecular weight of these two impurities as 276.0 [M-H] of unknown impurity corresponding to RRT=0.65 and 276.0 [M-H] of unknown impurity corresponding to RRT=0.65.

Based on these molecular weight, we scrutinize the different structures and finally reached to the conclusion to prepare 1-(3,4-Dichlorophenyl)-1,2,3,4-tetrahydronaphthalene (2) and 1-(3,4-Dichlorophenyl)-1,2-dihydronaphthalene (4).

For the preparation of 1-(3,4-Dichlorophenyl)-1,2,3,4-tetrahydronaphthalene (2), we experimented hydrogenation of Sertralone (1) using catalyst such as Raney Nickel, Palladium charcoal on carbon and found that best results obtained with 5% Palladium charcoal catalyst. Hence Sertralone (1) is hydrogenated in presence of 5% Pd/Charcoal catalyst at 2.0 kgf pressure at 30-35^{0}C resulted to give 1-(3,4-Dichlorophenyl)-1,2,3,4-tetrahydro naphthalene (2). This compound is further characterised by IR, ^{1}H-NMR and ^{13}C-NMR techniques and confirmed its structure as 1-(3,4-Dichlorophenyl)-1,2,3,4-tetrahydronaphthalene (2).

For the preparation of 1-(3,4-Dichlorophenyl)-1,2-dihydronaphthalene (4), we first reduced Sertralone (1) by using sodium borohydride as a reducing agent so that keto group gets converted into corresponding alcohol to get Sertralon-1-ol (3). This intermediate product Sertralon-1-ol (3) further dehydrated using sulphuric acid as dehydrating agent in toluene so that water formed is removed from the reaction mass by azeotropic distillation technique resulted to give 1-(3,4-Dichlorophenyl)-1,2-dihydronaphthalene (4). This compound is further characterised by IR, ^{1}H-NMR and ^{13}C-NMR techniques and confirmed its structure as 1-(3,4-Dichlorophenyl)-1,2-dihydronaphthalene (4).

In GC spiking study, we observed that compound 1-(3,4-Dichlorophenyl)-1,2,3,4-tetrahydro naphthalene (2) is same as corresponding impurity at RRT=0.65 and compound 1-(3,4-Dichlorophenyl)-1,2-dihydronaphthalene (4) is same as corresponding impurity at RRT=0.69. Hence, these two compounds are finally used as reference standards during GC analysis of Sertraline hydrochloride as a final drug as per pharmacopeia methods as known impurities.

CONCLUSION

In conclusion, the unknown impurities generated during preparation of sertraline hydrochloride are synthesized, characterised and identified as 1-(3,4-Dichlorophenyl)-1,2,3,4-tetrahydronaphthalene (2) corresponding to RRT=0.65 and 1-(3,4-Dichlorophenyl)-1,2-dihydronaphthalene (4) corresponding to RRT=0.69. Thus, these compounds 1-(3,4-Dichlorophenyl)-1,2,3,4-tetrahydronaphthalene (2) and 1-(3,4-Dichlorophenyl)-1,2-dihydronaphthalene (4) can be used as reference standards during GC analysis of Sertraline hydrochloride as a final drug as per pharmacopeia methods.

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REFERENCES

1. Veerle G, Katleen V. S, Damiaan D, Dieter D; Selective serotonin reuptake inhibitors as a novel class of immunosuppressants; International Immunopharmacology; Volume 20, Issue 1, May 2014, Pages 148–156
2. Janet E. A, Linda E. L, Patricia A. B and Kristan J. A; Selective serotonin reuptake inhibitor (SSRI) antidepressants, prolactin and breast cancer; Frontiers in oncology; December 2012 | Volume 2 | Article 177 | pages 1 - 9
3. Pohl RB., Wolkow RM., Clary CM. Sertraline in the treatment of panic disorder. A double-blind multicenter trial. *Am J Psychiatry.* 1998;155:1189–1195.
4. Katzelnick DJ., Kobak KA., Greist JH., Jefferson JW., Mantle JM., Serlin RC. Sertraline for social phobia: a double-blind, placebo-controlled, crossover study. *Am J Psychiatry.* 1995;152:1368–1371.
5. Greist JH., Jefferson JW., Kobak KA., et al. A one-year, double-blind, placebo-controlled fixed dose study of sertraline in the treatment of obsessive-compulsive disorder. *Int Clin Psychopharmacoi.* 1995;10:57–65.
6. Jeffrey V., Amir H. K; Generic Penetration in the Retail Antidepressant Market; Psychiatry (Edgemont); 2010; 7(6): 9–11
7. The United State Pharmacopoeia 39; sertraline hydrochloride monograph; 2016; volume 3, pp 5831-5833.
8. European pharmacopoeia 8.0; sertraline hydrochloride monograph 1705; 2011; volume 3, pp 3210-3212.