RJC
http://www.rasayanjournal.com

RASĀYAN *J. Chem.*
Vol.3, No.4 (2010), 677-680
ISSN: 0974-1496
CODEN: RJCABP

IDENTIFICATION, ISOLATION, SYNTHESIS AND CHARACTERIZATION OF PRINCIPAL OXIDATION IMPURITIES IN QUETIAPINE

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ABSTRACT

Two oxidation products of Quetiapine hemifumarate (**IV**) were identified, isolated and characterized in addition to several known impurities during stability studies. These structures were verified by synthesis of the impurities and comparison of the spectra and chromatographic (HPLC and TLC) retention data of the isolated and synthesized materials.

Keywords: Quetiapine, Quetiapine *N*-oxide, Quetiapine *S*-oxide, Prep HPLC, Characterization.

INTRODUCTION

Quetiapine (**I**) is a psychoactive organic compound that acts as an antagonist for multiple neurotransmitter receptor sites, including serotonin ($5HT_{1A}$; $5HT_{2A}$), dopamine (D_1; D_2), histamine (H_1) and adrenaline (Alpha 1; Alpha 2), in the brain and acts as an antipsychotic agent reportedly useful for treating, among other things, schizophrenia[1]. Quetiapine has a lower affinity for D_2 receptors than dopamine itself, leading to an intermittent D_2 blockade, and may contribute to the excellent tolerability profile of this substance. It was hypothesized that Quetiapine may act on depression, through its antagonism of 5-HT_{2A} receptors, and on mania through its antagonism of D_2 receptors[2]. Quetiapine was found to be effective in the treatment of acute bipolar mania, both as monotherapy and in combination with other mood stabilisers[3], as well as monotherapy in acute bipolar depression[4]. Despite this, to our knowledge, there are very few published experiences with regard to long-term Quetiapine monotherapy in schizoaffective disorder, bipolar type (SAD) and bipolar disorder (BPD)[5].

During the stability studies of Quetiapine hemifumarate (**II**) in the laboratory, several batches has been analyzed for purity by HPLC. Besides several known impurities[6-8], two additional compounds at level 0.1% were detected by ion-pair reversed-phase high-performance liquid chromatography (HPLC). As per the stringent regulatory requirements recommended by ICH the impurities ≥0.1 % must be identified and characterised[9]. A thorough study has been under taken to synthesize and characterize these identified substances.

EXPERIMENTAL

Thin-layer chromatography (TLC) were run on silica gel 60 F_{254} precoated plates (0.25 mm, Merck, Art.5554) and spots were visualized inside an UV cabinet under short UV. Infrared spectra were recorded on Perkin Elmer Spectrum FT-IR Spectrometer by using 1% potassium bromide pellet. ^1H and ^{13}C NMR spectra were recorded on Bruker 300 MHz Advance NMR spectrometer at 300 MHz for ^1H NMR and 75 MHz for ^{13}C NMR with TMS as an internal standard. Mass spectra were obtained using a Agilent 1100 Series LC-MSD-TRAP-SL system. All other reagents were purchased from Lancaster (Germany) and S.D.Fine Chemicals, Mumbai. The solvents and reagents were used without purification.

2-[2-(4-Dibenzo[*b,f*][1,4]thiazepin-11-yl-piperazin-1-yl-1-oxide)ethoxy]ethanol (Quetiapine *N*-oxide, III)

To a solution of Quetiapine hemifumarate (**II,** 22 g**,** 25 mmol) in chloroform (100 mL) and water (100 mL) was added 10% $NaHCO_3$ (100 mL) to adjust the pH to 8. The organic layer was separated, washed with DM water (2 X 100 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure at less than 50^0C. The obtained Quetiapine (**I,** 9.57 g, 25 mmol) residue was dissolved in methanol (200 mL) and sodium periodate (1.16 mmol) was then added at ambient temperature. The reaction mass was stirred at the same temperature for 48 h. The progress of the reaction was monitored by TLC (chloroform: methanol-9:1). The resulting slurry was filtered to remove inorganic materials. The filtrate was concentrated under reduced pressure at less than 50^0C and acetonitrile (100 mL) was added to the obtained residue under stirring. The separated solid was filtered. The wet cake was purified by slurry wash with methanol (2 x 100 mL) and dried at 40^0C to isolate compound **III** as a white solid. Yield-8.5 g; IR (KBr, cm^{-1}): 3435 (OH), 3070 (Ar-H), 2918, 2872 (Aliphatic-H), 1596, 1574, 1559 (C=C/C=N), 1457, 1441, 1415 (Aliphatic-H bending), 1304 (C-N), 1263 (C-O-C, asymm. stretching), 1123, 1067, 1032 (C-O-C, symm. stretching), 788, 767, 744 (Ar-H bending), 670, 653, 595 (C-S); ^{1}H NMR(DMSO-d_6, δ ppm): 7.56-7.59 (m, 1H, Ar-H), 7.46-7.50 (m, 3H, Ar-H), 7.38-7.41 (dd, J = 7.7 & 1.4 Hz, 1H, Ar-H), 7.18-7.24 (m, 1H, Ar-H), 7.01-7.04 (dd, J = 7.0 & 1.4 Hz, 1H, Ar-H), 6.90-6.95 (m, 1H, Ar-H), 5.18 (br, s, 1H, D_2O exchangeable, OH), 3.97 (m, 2H, OCH_2), 3.97 (m, 2H, OCH_2), 3.35-3.68 (m, 12H, 5 X N-CH_2 +OCH_2), 3.01-3.11 3.01 - 3.11 (m, 2H, OCH_2OH); ^{13}C NMR(DMSO-d_6, δ ppm): 159.70, 148.33, 138.76, 133.16, 132.06 (2C), 131.50, 129.32, 129.06 (2C), 127.29, 125.06, 122.92, 72.11, 69.42, 63.85 (2C), 63.58, 59.98; DIP MS: *m/z* (%) 400 $[M+H]^+$(83), 422 $[M+Na]^+$(25).

2-{2-[4-(5-Oxo-5*H*-5λ^4-dibenzo[*b,f*][1,4]thiazepin-11-yl)-piperazin-1-yl]ethoxy}ethanol (Quetiapine *S*-oxide, IV).

To a mechanically stirred 500 mL round-bottom flask containing Quetiapine hemifumarate (**II**, 9.71 g, 11 mmol) was added methanol (200 mL). After 15 min, sodium tungstate dihydrate (4.8 g, 14. 6 mmol) was added to the reaction mixture and , after 30 min, hydrogen peroxide (50%, 0.68 g, 10 mmol) was added. The reaction mass was stirred for 24 h. The progress of the reaction was monitored by TLC (chloroform: methanol-9:1). The resulting solution was quenched with $Na_2S_2O_3$ (1 g, 6.32 mmol). The reaction mass was concentrated under reduced pressure at less than 50^0C. The obtained residue was partitioned between chloroform (100 mL) and water (100 mL). The organic layer was washed with DM water (100 mL), dried, and distilled off. The resulting residue was subjected to prep-HPLC to get oxidized product **IV**. Yield-4g; IR (KBr, cm^{-1}): 3412 (OH), 2989, 2956, 2920 (Aliphatic-H), 1712, 1668, 1578, 1558 (C=C/C=N), 1403 (Aliphatic-H bending), 1268(C-O-C, asymm. stretching), 1158, 1119 (C-N), 1040 (C-O-C, symm stretching), 1016 (S=O), 881, 837 (Ar-H bending), 657, 617 (C-S); ^{1}H NMR(DMSO-d_6, δ ppm): 7.56-7.79 (m, 2H, Ar-H), 7.28-7.49 (m, 4H, Ar-H), 7.18 (t, J = 7.5 Hz, 1H, Ar-H), 6.97-7.07 (m, 1H, Ar-H), 3.41-3.56 (m, 6H, 3 x OCH_2), 2.48-2.55 (m, 10H, 5 X N-CH_2); ^{13}C NMR(DMSO-d_6, δ ppm): 157.00, 147.35, 142.55, 135.70, 132.05, 130.67, 130.56, 128.48, 124.73, 123.42, 122.19, 119.77, 119.00, 72.24, 68.21, 60.26, 57.17, 52.77, 45.28; DIP MS: *m/z* (%) 400 $[M+H]^+$(83), 422 $[M+Na]^+$(5).

RESULTS AND DISCUSSION

In the stability studies, the purity of the subjected materials was analyzed by HPLC, in which two unknown peaks were observed. LC-MS analysis showed both peaks having m/z values 400 (M+H), where as Quetiapine is m/z 383. These oxidized products were isolated from material used for stability studies, using normal-phase preparative HPLC. ^{1}H and ^{13}C NMR and mass spectrometric investigations revealed the structures of the oxidative products to be 2-[2-(4-dibenzo[*b,f*] [1,4]thiazepin-11-yl-piperazin-1-yl-1-oxide)ethoxy]ethanol (Quetiapine *N*-oxide, **III**, Rf-0.6, MeOH : chloroform-1:9) and 2-{2-[4-(5-oxo-5*H*-5λ^4-dibenzo[*b,f*][1,4]thiazepin-11-yl)-piperazin-1-yl]ethoxy}ethanol (Quetiapine *S*-oxide, **IV**, Rf-0.7, MeOH : chloroform-1:9).

Oxidative product **III** was synthesized by reacting **I** with sodium periodate in methanol at ambient temperature. The DIP mass spectrum of **III** exhibited a molecular ion peak at *m/z* 400 (M+H), which has 16 units more than Quetiapine. In the IR spectrum, the presences of bending vibrations of C-S-C are in the region 670-595 and absence of S=O stretching has confirmed that sulfur is not oxidized. In addition, in the ^{1}H NMR spectrum, unchanging of aromatic region δ 6.9-7.59 indicating neither S nor N of benzodiazepine moiety is not oxidized and aliphatic region down shielded to δ 3.01-3.97. Especially, protons of three methylene moieties attached to first position of the piperazine were down shielded to δ 3.35-3.68 (6H) from δ 2.50-2.54 (6H).[6] Further, ^{13}C NMR revealed that three carbons attached to first position of the piperazine were down shielded to δ 63.85 and 69.42 from δ 46.7 and 57.8 respectively[6]. The spectral data obtained was confirming the assigned structure **III.**

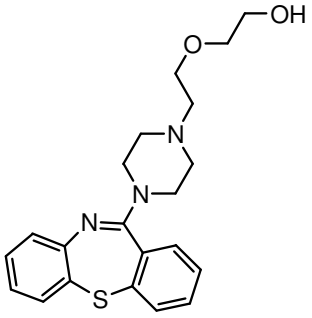
Quetiapine hemifumarate (**II**) is oxidized with hydrogen peroxide in methanol in the presence of sodium tungstate dihydrate to produce oxidized product **IV.** The DIP mass spectrum of **IV** displayed a molecular ion peak at *m/z* 400 (M+H), which is similar to oxidized product **III**. The IR spectrum of **IV** exhibits characteristic S=O stretching at 1016 in addition to C-S-C stretching (657-617 cm^{-1}) indicating oxidation of sulfur. The ^{1}H NMR spectrum revealed down shield of aromatic region to δ 6.97-7.79 and aliphatic region remains same as **II**[6]. Further, signals in the ^{13}C NMR spectrum for C-14 and C-18 at δ128.48 and 119.77 indicating up shield of carbons due to oxidation of sulfur, however, corresponding values for compound **II** are δ132.1 and 132.9.[6] The spectral data obtained was confirming the assigned structure **IV**.

CONCLUSION

In summary, we have developed a method for selective oxidation of Quetiapine to prepare oxidized products Quetiapine N-oxide and Quetiapine S-oxide by using sodium periodate in methanol and hydrogen peroxide in methanol in the presence of sodium tungstate dihydrate respectively.

ACKNOWLEDGMENTS

The authors express their thanks to colleagues in the Analytical Division of Matrix Laboratories Limited, for providing analytical and spectral data.



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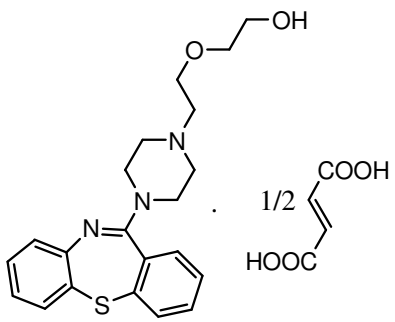
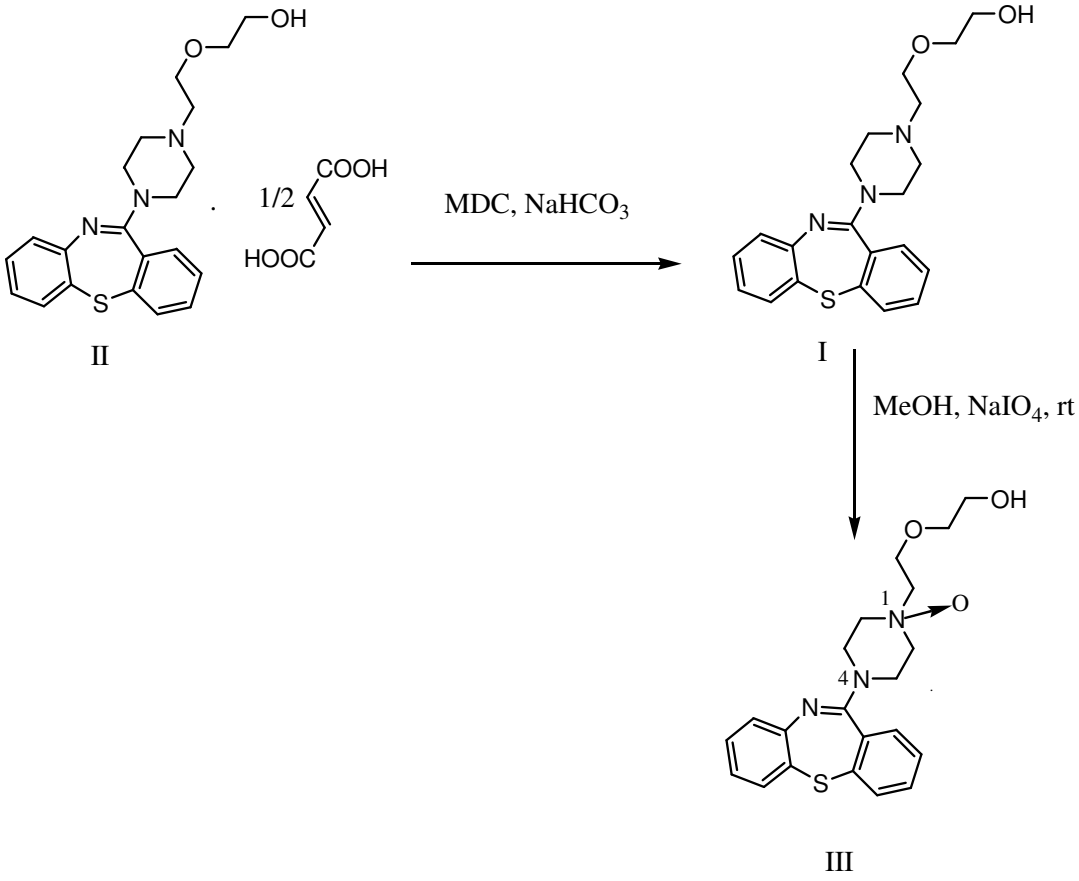


II

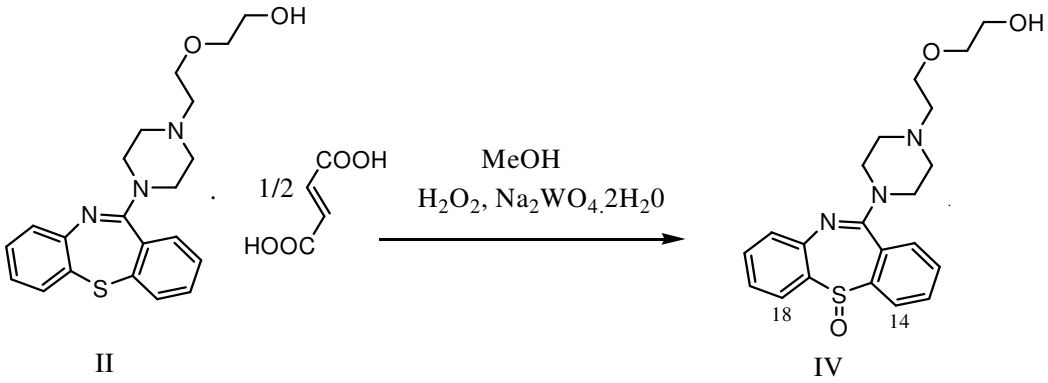
REFERENCES

1. Merch Index, 13th Ed., 8130, 2001.
2. L. N. Yatham, J. M. Goldstein, E. Vieta, C. L. Bowden, H. Grunze and R. M. Post, *J Clin Psychiatry,* **66**, 40 (2005).
3. E. Vieta, J. Mullen, M. Brecher, B. Paulsson and M. Jones, *Curr Med Res Opin* **21**, 923 (2005).
4. J. R. Calabrese, Jr. PE. Keck, W. Macfadden, M. Minkwitz, T. A. Ketter and R. H. Weisler, *Am J Psychiatry,* **162***,* 1341(2005).
5. S. N. Ghaemi and J. J. Katzow, *Ann Clin Psychiatry,* **11,** 137 (1999).
6. Ch. Bharathi, K. J. Prabahar, Ch. S. Prasad, M. Srinivasa Rao, G. N. Trinadhachary, V. K. Handa, R. Dandala and A. Naidu, *Pharmazie*, **63**, 14 (2008).

7. E. U. Stolarczyk, K. Kaczmarek, Kamil Eksanow, M. Kubiszewski, M. Glice, and A. Kutner, *Pharmaceutical Development and Technology* , **14**, 27 (2009).
8. F. Belal, A. Elbrashy, M. Eid and J. J. Nasr, *Journal of Liquid Chromatography & Related Technologies*, **31**, 1283 (2008).
9. ICH Guideline Q3A (R), Impurities in New Drug Substances, February 7, 2002.



Scheme-1



Scheme-2

[RJC- 657/2010]