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ChemTech

nternational Journal of ChemTech Research
CODEN(USA): IJCRGG ISSN : 0974-4290
Vol.5, No.5, pp 2216-2220, July-Sept 2013

Identification, Isolation, Synthesis And Characterization Of An Impurity In Quetiapine Bulk Drug Substance

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Abstract: Novel Quetiapine impurity, named *N*-methyl-2-pyrrolidinone (NMP) impurity, have been identified, isolated and characterized on the basis of spectroscopic data.
Keywords: Quetiapine, *N*-methyl-2-pyrrolidinone impurity, preparative High-performance liquid chromatography (HPLC), characterization.

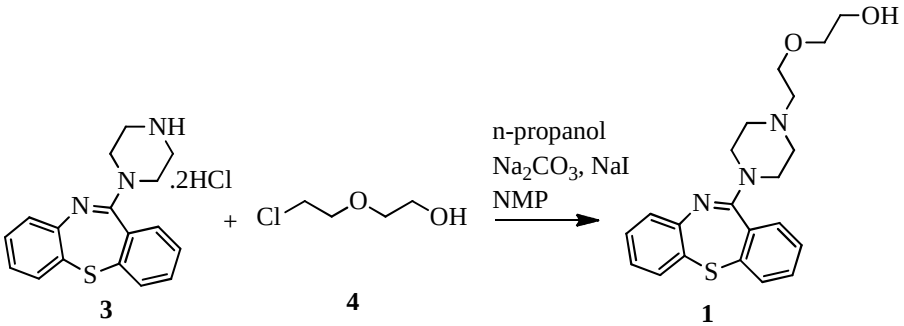
Introduction:

Quetiapine (**1**) 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 stabilizers [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].

Related substances in the form of by-products or process impurities are possible during the manufacturing process and storage of the drug substance. The acceptance criteria for these impurities are stringent and based on the guidelines laid down by the International Conference on Harmonization (ICH) and pharmacopeia. As per the stringent regulatory requirements recommended by ICH, the impurities ≥0.1 % must be identified and characterized [6-7].

The literature survey revealed synthetic methods for quetiapine hemifumarate [8]. It was synthesized according to the Scheme-1, with slight modifications to make it simpler and commercially viable. During the process development of quetiapine hemifumarate (**2**) in the laboratory by reacting 11-piperazinyldibenzo[*b*,*f*][1,4] thiazepine dihydrochloride (**3**) with 2-chloroethoxyethanol (**4**) in n-propanol containing sodium carbonate,

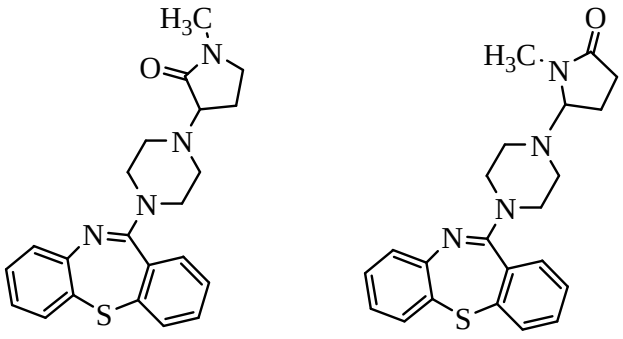
sodium iodide and *N*-methyl-2-pyrrolidone at reflux for 24h, several batches have been analyzed for purity by HPLC. Besides several known impurities, there were identified by HPLC, one of the impurity was found not to be reported previously [9-12]. A thorough study has been under taken to synthesize and characterize this unknown impurity.



Scheme-1:Synthesis of Quetiapine (**1**)

The unknown impurity has been isolated by preparative HPLC and was characterized by mass, NMR and IR spectral data. The obtained data of the isolated impurity has been compared with the quetiapine data [9]. The mass spectral data indicated an even molecular mass ($C_{22}H_{24}N_4OS$ - 392.52 amu) for the impurity. This implies the existence of even number of nitrogen atoms [13]. The quetiapine molecule contains three nitrogen atoms belonging to 4-(dibenzo[*b,f*][1,4]thiazepin-11-yl)-piperazin-1-yl moiety. The base peak at m/z 295.11 ($C_{17}H_{17}N_3S$) in mass spectra indicated the presence of 4-(dibenzo[*b,f*][1,4]thiazepin-11-yl)-piperazin-1-yl moiety in the impurity. Further, the presence of 4-(dibenzo[*b,f*][1,4]thiazepin-11-yl)-piperazin-1-yl moiety is confirmed by ^{1}H-NMR & ^{13}C-NMR by showing peaks at δ 6.86-7.48 for the aromatic region and δ 3.30-3.44 (4H, m) & 2.39-2.60 (4H, m) for piperazine methylenes which are similar to quetiapine data [9]. It is, therefore, noted that there must be an additional nitrogen atom present in the side chain which contributes to the even molecular mass of the impurity. However, the rest of the aliphatic region of the impurity looked more complex than expected in the NMR spectra.

The quetiapine has no carbonyl peak in the IR spectrum and the impurity on the contrary exhibits a peak at 1690 cm^{-1} (strong C=O stretching) due to presence of carbonyl group. The ^{1}H-NMR spectra of quetiapine has four methylene groups in the side chain apart from the piperazine peaks, whereas the impurity spectra showing peaks at δ 4.44 (1H), 2.16-2.25 (2H), 1.90-1.95(2H) and 2.70-2.73 (3H). In addition, in the ^{13}C-NMR spectra, the peaks to be assigned are at δ 173.56, 78.80, 29.26, 27.49 and 17.48. The DEPT experiment evident that the peat at δ 173.56 is quaternary, δ 78.80 is methine, δ 29.26 is methylene, δ 27.49 is methylene and δ 17.48 is methyl respectively. Based on the preliminary data from the mass, IR, ^{1}H-NMR and ^{13}C-NMR spectra, these peaks belongs to 1-methyl-pyrrolidin-2-one and is attached to 4-(dibenzo[*b,f*][1,4]thiazepin-11-yl)-piperazin-1-yl moiety. Then the unknown impurity may be either structure-A (3-C-N bond formation) or structure-B (5-C-N bond formation).



Stucture-A Stucture-B

To confirm the unambiguously the position of the C-N bond formation (C-3 in structure A vs C-5 in structure B), detailed study of the 2D-NMR spectra for the impurity has been under taken. The HSQC of the impurity has important correlation (i) 4.44: 78.80 (ii)2.16-2.25:17.48 and (iii) 1.90-1.95: 29.26. The COSY spectrum has shown clear spin system of 4.44 ppm, 1.90-1.95 ppm and 2.16-2.25 ppm. The HMBC has correlations of 4.44 ppm with 17.48 ppm, 29.26ppm, 45.20ppm, 173.56 and 2.70-2.73 with 78.80ppm, 173.56 ppm indicated that the presence of 1-methyl-2-pyrrolidinone-3-yl moiety in the impurity and the correct structure for the NMP impurity is structure-B. The NMR assignments were tabulated in Table-1 and COSY and HMBC correlations were shown in figure-1. The long range correlations of ^{1}H and ^{13}C-NMR were obtained by HMBC experiment. H-16 has correlation with C-15, 15', C-17, C-18, and C-19. Similarly, the H-20 showed the correlations with C-16 and C-19.

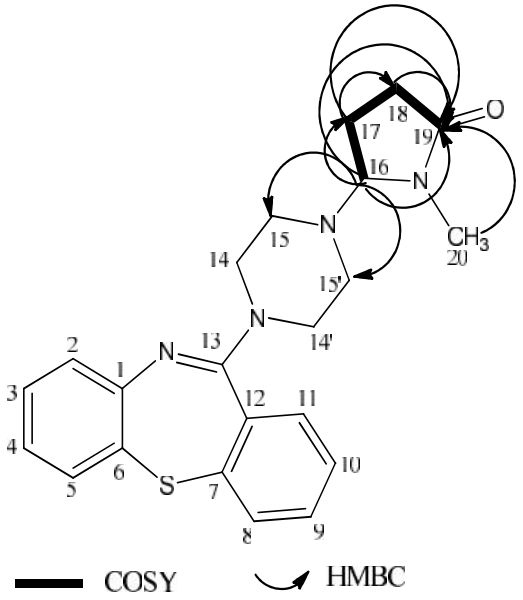


Figure-1: The COSY and HMBC correlations

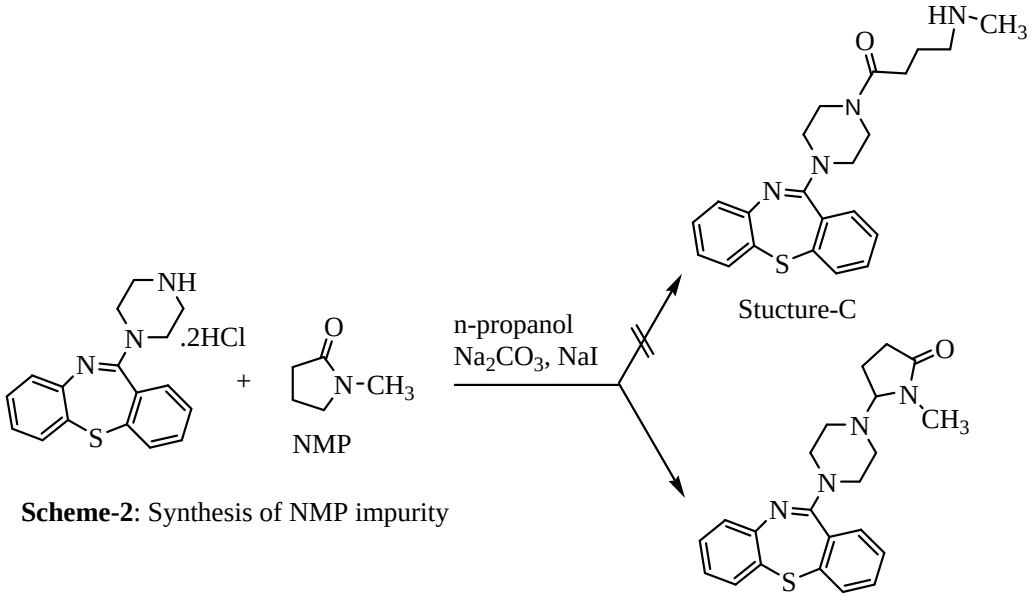
Table-1.

Position	^{1}H	δ (ppm)	J(Hz)[1]	^{13}C	DEPT
1	-	-	-	148.56	-
2	1H	6.97-7.00	m	124.94	CH
3	1H	6.86-6.92	m	122.48	CH
4	1H	7.16-7.21	m	128.88	CH
5	1H	7.35-7.48	m	131.20	CH
6	-	-	-	127.17	-
7	-	-	-	133.52	-
8	1H	7.53-7.56	m	131.90	CH
9	1H	7.35-7.48	m	129.03	CH
10	1H	7.35-7.48	m	129.20	CH
11	1H	7.35-7.48	m	131.95	CH
12	-	-	-	138.63	-
13	-	-	-	160.08	-
14,14'	4H	3.30-3.44	m	46.35	CH_2
15,15'	4H	2.39-2.60	m	45.20	CH_2
16	1H	4.44	t(5.1)	78.80	CH
17	2H	2.16-2.25	m	17.48	CH_2
18	2H	1.90-1.95	m	29.26	CH_2
19	-	-	-	173.56	-
20	3H	2.70-2.73	m	27.49	CH_3

t-triplet, m-multiplet.

[1] ^{1}H-^{1}H Coupling constants.

To confirm the proposed structure, the impurity was synthesized independently by treating dihydrochloride salt of compound **3** [8] with *N*-methyl pyrrolidone in presence of base at reflux in multi-gram scale (Scheme-2) with out formation of compound of structure-C.



Scheme-2: Synthesis of NMP impurity

The formation of unusual 5-C-N bond probes us to search the literature. Surprisingly, the literature survey revealed the formation of 5-C-C [14-16] and 5-C-N [17] bonds in 1-substututed-pyrrolidin-2-one. The above experiment conform that nucleophilic substitution takes place at C-5 position of 1-methyl-pyrrolidin-2-one and not at C-3 position. Furthermore, δ 4.44 is reported for the 5-CH and δ 3.30-3.50 is reported for the 3-CH [17]. At the moment, we are unable to explain the mechanism. However, the assumed mechanism has been disclosed [17]. The mechanism is probably initiated by generation of the immonium species (Figure-2) from *N*-methyl-2-pyrrolidinone, which would readily undergo nucleophilic addition with piperazine derivative.

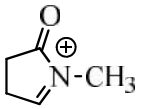


Figure-2: Immonium species

Experimental

Infrared spectra were recorded on a Perkin-Elmer Spectrum FT-IR spectrometer by using 1% potassium bromide pellet. All NMR experiments were performed on a Bruker AVANCE-300 instrument with a 5-m BBO probe head equipped with shielded Z-gradient coil at 298 K using solutions of 5 mg (for ^{1}H-NMR) and 30 mg (for ^{13}C-NMR) of the compound dissolved in 0.6 ml of $CDCl_3$ / DMSO-d_6. The data were collected and processed by XWIN-NMR software (Bruker) running on a PC with Microsoft Windowsxp. The ^{1}H-NMR analysis, 16 transients were acquired with a 1-s-relaxation delay using 32 K data points. The 90°pulse duration was of 11 μs and spectral width 6.000 kHz. The ^{13}C-NMR and DEPT experiments were carried out with a spectral width of 16.500 kHz using 64 K data points. The two-dimensional experiments were performed using Bruker standard pulse sequences and parameters.The ^{1}H–^{1}H bond correlations confirmed by gCOSY experiment (cosygpqf). The protonated carbon positions were confirmed by a gHSQC experiment (hsqcetgpsi2). The nonprotonated carbons were confirmed by a gHMBC experiment (hmbcgplpndqf). The ^{1}H chemical shifts are reported in ppm with reference to tetramethylsilane (δ0.0 ppm). The ^{13}C chemical shifts were referenced to the central peak of the solvent molecule $CDCl_3$ (δ 77.00 ppm) or DMSO-d_6 (δ 39.50 ppm). All mass spectra are recorded on Agilent 1100 Series LC-MSD-TRAP-SL system. The electrospray ion source operated in positive

mode with a needle voltage of 1500V and a cone voltage of 4500V in the scan mass range 150–650 (*m*/z). Nitrogen was used as nebulizer and curtain gas. Mass spectra were obtained using a Agilent 1100 Series LC-MSD-TRAP-SL system. The sample introduced via the Direct Inlet Probe (DIP).

4-(Dibenzo[*b*,*f*][1,4]thiazepin-11-yl)-1-(*N*-methylpyrrolidinone-5-yl)piperazine (Structure B): The 11-piperazinyldibenzo[*b*,*f*][1,4]thiazepine dihydrochloride (25 mmole), sodium carbonate (150 mmole), sodium iodide (1 mmole) and were combined together in n-propanol (60 mL) and *N*-methyl pyrrolidone (15 mL). The reaction was heated at reflux for 24 hours. Ethyl acetate (75 mL) was added and the reaction washed with water (2 X 250 mL). The organic phase was dried over magnesium sulfate and the solvent removed in vacuo to give oil. The obtained oil was purified through silicagel column using methanol-chloroform (2:98) as eluent to afford a light brown colour 4-(dibenzo[b,f][1,4]thiazepin-11-yl)-1-(*N*-methylpyrrolidinone-5-yl)piperazine (Structure B). IR (KBr, cm-^{1})-3051, 2926, 2849, 1690, 1598, 1575, 1454, 1422, 1397, 1307, 1248, 1144, 1018, 1005, 989, 764,743, 688, 669, 657; ^{1}H NMR (300 MHz, DMSO-d_6), ^{13}C NMR (75 MHz, DMSO-d_6) and DEPT data: see Table-1; DIP MS: m/z 393 (M+H), 296.

Acknowledgments

The authors thank the management of Mylan Laboratories Ltd., for supporting this work.

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