Eszopiclone (Lunesta™): An Analytical Profile

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ABSTRACT: Eszopiclone (Lunesta™) is a nonbenzodiazepine hypnotic/sedative prescribed for treatment of insomnia. Analytical data (gas chromatography, mass spectrometry, infrared spectroscopy, ultra performance liquid chromatography, and proton and carbon-13 nuclear magnetic resonance spectroscopy) for eszopiclone are presented.

KEYWORDS: Lunesta™, Eszopiclone, Hypnotic, Sedative, Forensic Chemistry

Introduction

The DEA Special Testing and Research Laboratory recently received a sample of eszopiclone (Figure 1) to add to its reference standards collection. Eszopiclone (the active "S" enantiomer of zopiclone) is a nonbenzodiazepine hypnotic/sedative prescribed for treatment of chronic (long-term) insomnia. It is currently marketed in tablet form as Lunesta™, in concentrations of 1, 2, or 3 milligrams per tablet (see Photo 1) (1). Although it has a reduced potential for abuse versus classic benzodiazepine hypnotic/sedatives, it is a Schedule IV controlled substance, and federal law restricts it to prescription use. Based upon its potential for abuse, and the limited literature available concerning its analysis, herein are provided GC, GC/MS, FTIR-ATR, UPLC, and ^{1}H- and ^{13}C-NMR data for eszopiclone.

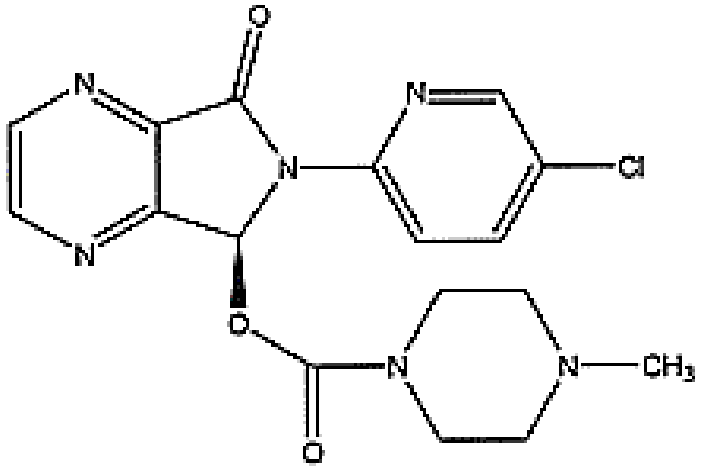

Figure 1. Eszopiclone.

Photo 1. 3 Milligram Tablet
(Note: Diameter is 6.4 Millimeters).

Experimental and Discussion

Eszopiclone
Source: Sepracor Canada, LTD. (Windsor, Nova Scotia, Canada)
Lot Number / Purity: 029-0014 RS / 99.9 %
Chemical Formula / CAS Number: $C_{17}H_{17}ClN_6O_3$ / [138729-47-2]
Molecular Weight: 388.81 amu
Melting Point: 202 - 203 ^{O}C (2)
Solubility: [Chloroform: Soluble; Methanol: Somewhat Soluble; Deionized H_2O: Somewhat Soluble]

Gas Chromatography (GC)

Instrument:	Agilent 6890 equipped with a Flame Ionization Detector (FID)
Column:	DB-1, 30 m x 0.25 mm I.D, 0.25 μm film thickness
Injector Temperature:	280 ^{O}C
Oven Temperature:	100 ^{O}C for 1 minute, 12 ^{O}C/minute to 280 ^{O}C, 7 minute hold
Carrier Gas:	Hydrogen at 1.1 mL/minute, split ratio = 25:1

Approximately 8.95 milligrams and 8.63 milligrams of eszopiclone were added to 2 mL of methanol and 2 mL of chloroform, respectively, and vortexed until dissolved; eszopiclone took longer to dissolve in methanol than in chloroform. Utilizing the described experimental parameters, both solutions displayed a major chromatographic peak at 21.14 minutes. In addition, both solutions displayed the same chromatographic pattern with minor early eluting peaks - possibly due to eszopiclone breakdown. The chromatogram of the chloroform solution is illustrated in Figure 2.

Gas Chromatography/Mass Spectrometry (GC/MS)

Instrument:	Agilent 6890 Gas Chromatograph equipped with an Agilent 5973 Mass Selective Detector (MSD)
Column:	DB-1, 30 m x 0.25 mm I.D., 0.25 μm film thickness
Injector Temperature:	280 ^{O}C
Oven Temperature:	100 ^{O}C for 2 minutes, 14 ^{O}C/minute to 300 ^{O}C, 10 minute hold
Carrier Gas:	Helium at 1.0 mL/minute, split ratio = 25:1
Scan Range:	34-550 amu
Electron Ionization:	70 eV

In methanol, one major peak at approximately 18 minutes was observed in the Total Ion Chromatogram (TIC) (Figure 3), with minor early eluting peaks as noted above. The fragmentation pattern shows a base peak at *m/z* 143 with other mass fragments at *m/z* 245, 99, 112, 217, 139, and 56 (Figure 4). The molecular ion was not detected.

Fourier Transform Infrared Spectroscopy - Attenuated Total Reflectance (FTIR-ATR)
Instrument: Thermo-Nicolet Nexus 670 FTIR Spectrometer equipped with SensIR Dura-Scope Attenuated Total Reflectance (ATR) Accessory (1-Bounce Diamond/KRS-5 Focusing)

The eszopiclone standard was analyzed directly without preparation. Figure 5 (full spectrum) and Figure 6 (fingerprint region) illustrate the baseline-corrected spectra. The following is a list of assignments and corresponding wavenumbers (cm^{-1}): Aromatic C-H stretch (3077), aliphatic C-H stretch (2941, 2837, 2789), ester carbonyl stretch (1730), amide carbonyl stretch (1713), CH_2 bend (1462), CH_3 bend (1417), tertiary aromatic amine (1370), aliphatic C-N (1290,1238,1140), C-O stretch (1086), and C-Cl stretch (848) (3).

Ultra Performance Liquid Chromatography (UPLC)

Instrument:	Waters ACQUITY Ultra Performance Liquid Chromatograph (UPLC) equipped with Waters 2996 Photo Diode Array (PDA) Detector
Column:	2.1 mm x 100 mm Waters ACQUITY UPLC BEH C18, 1.7 µm
Mobile Phase:	A: 100 mM Phosphate buffer, pH 1.8; B: Acetonitrile
Flow Rate:	0.43 mL/minute
Linear Gradient:	98 % to 35 % A over 10 minutes, 35 % A for 2 minutes

A 100 mM phosphate buffer, pH 1.8, was added to 2.32 milligrams of eszopiclone until a 25.0 mL final volume was obtained. The solution was then sonicated for 15 minutes. Utilizing the above parameters, one peak at a retention time of 3.73 minutes was observed (Figure 7). Figure 8 illustrates the UV spectrum between the wavelengths 220 - 340 nm. The maximum UV absorbance is 301 nm.

Nuclear Magnetic Resonance (NMR) Spectroscopy

^{1}H- and ^{13}C-NMR spectra (see Figures 9 and 10, respectively) were acquired on a Varian Mercury *Plus* 400 MHz instrument using a Nalorac 5 mm indirect detect pulse field gradient (PFG) probe at 25 ^{O}C. (^{1}H parameters: Number of scans (nt) = 8, pulse width (pw) = 45 ^{O}, relaxation delay (d1) = 5 s, acquisition time (at) = 2.5 s; ^{13}C parameters: nt = 4098, pw = 45 ^{O}, d1 = 1 s, at = 1.3 s, complete proton decoupling). Spectra were processed using ACD's *SpecManager* software (Applied Chemistry Development Inc.©, Toronto, Canada). Eszopiclone was prepared in $CDCl_3$ containing 0.05 % v/v tetramethylsilane (TMS; Aldrich Chemical Co., Milwaukee, WI) at 16.84 mg/mL. Chemical shifts (δ) are reported in parts per million (ppm) using TMS (0.0 ppm) as the reference standard. ^{1}H data are reported as follows: Chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant, number of protons present. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.90 (d, *J* = 2.5 Hz, 1H), 8.85 (d, *J* = 2.5 Hz, 1H), 8.52 (d, *J* = 8.9 Hz, 1H), 8.40 (d, *J* = 2.4 Hz, 1H), 8.02 (s, 1H), 7.80 (dod, *J* = 8.9, 2.5 Hz, 1H), 3.65 (br m, 1H), 3.54 (br m, 1H), 3.25 (br s, 2H), 2.42 (br m, 2H), 2.26 (s, 3H), 2.22 (br m, 1H), 2.05 (br m, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.4, 162.9, 155.6, 153.4, 148.4, 147.8, 146.8, 143.9, 138.1, 133.4, 128.3, 116.1, 79.1, 54.5, 52.3, 46.1, 44.1.

Acknowledgements

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References

1. Material Safety Data Sheet. Lunesta™ Tablets, Sepracor Inc., Marlborough, MA:2005, p. 1.

2. Material Safety Data Sheet. Lunesta™ Tablets, Sepracor Inc., Marlborough, MA:2005, p. 6.

3. Sepracor Inc., Marlborough, MA. Personal communication, May, 2006.

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[Figures 2 - 10 Follow.]

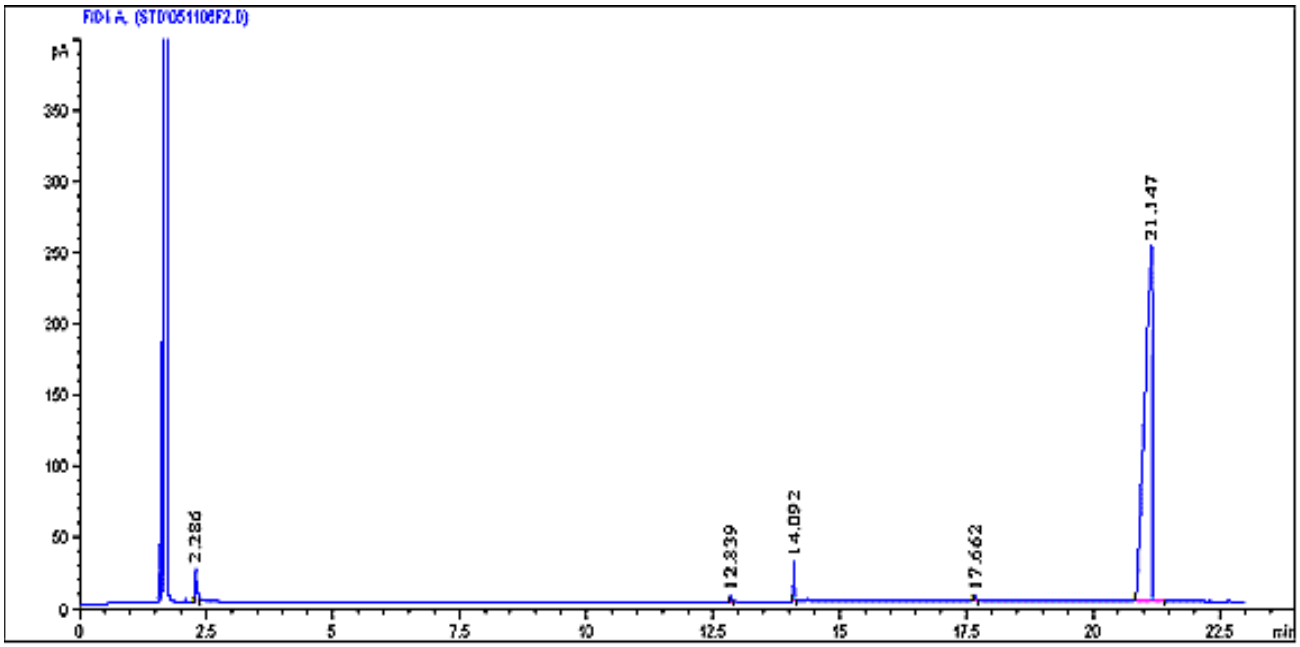

Figure 2. Gas Chromatogram of Eszopiclone in Chloroform.

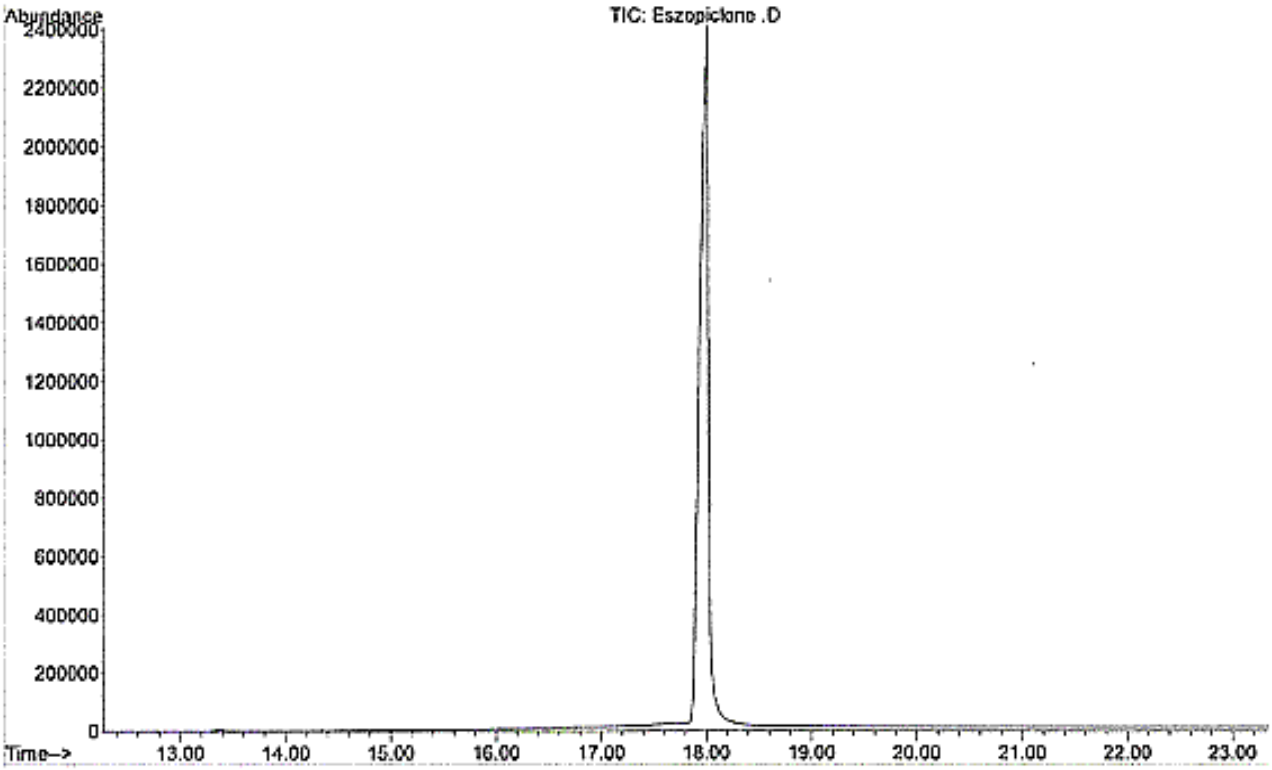

Figure 3. GC/MSD Total Ion Chromatogram of Eszopiclone.

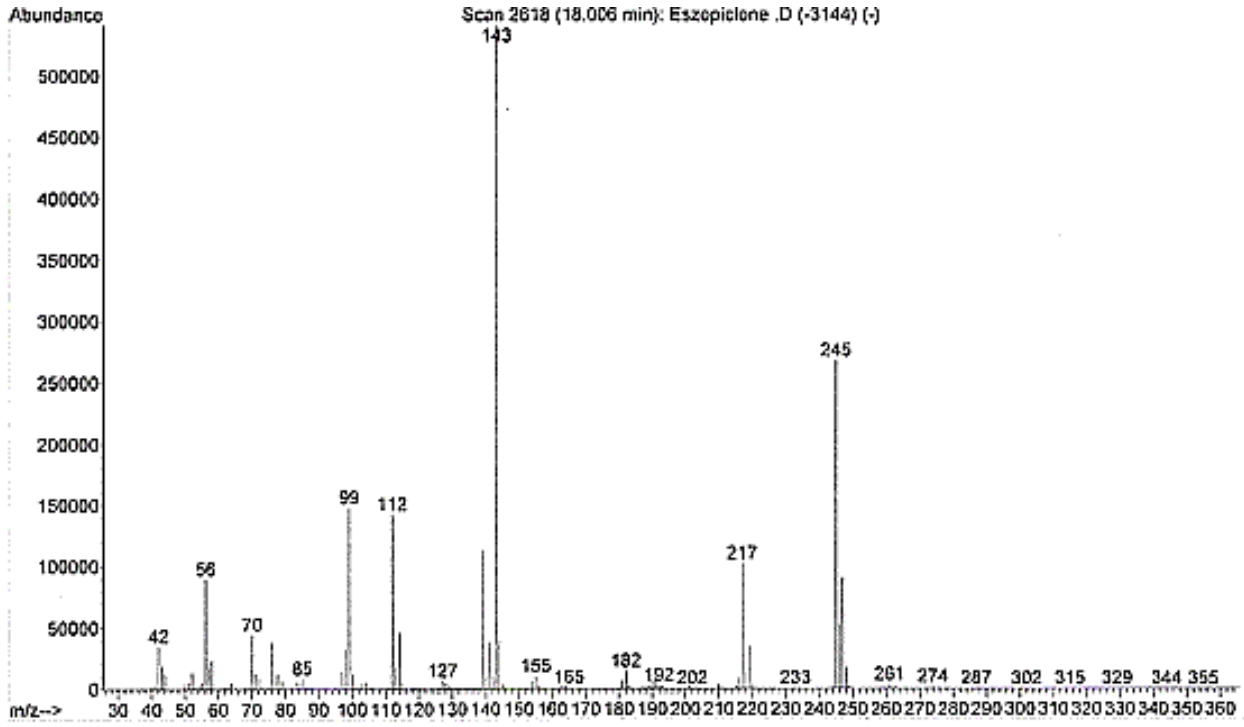

Figure 4. Electron Ionization Mass Spectrum of Eszopiclone.

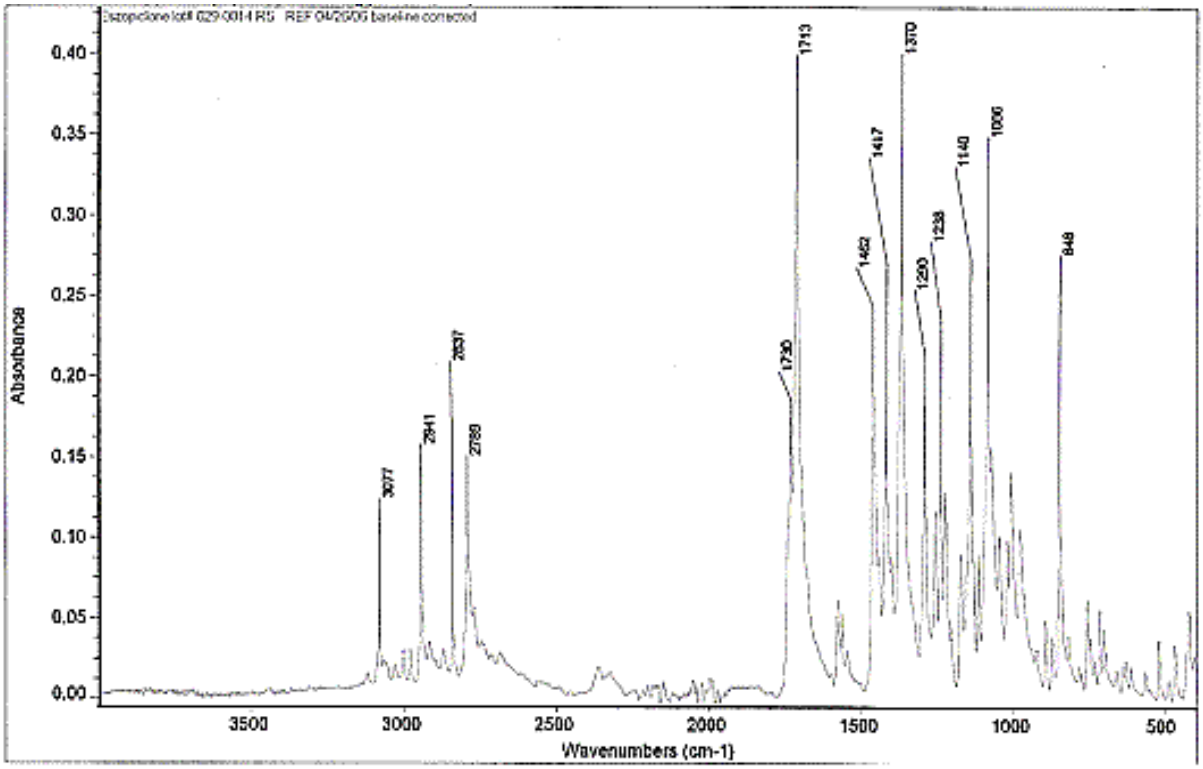

Figure 5. FTIR-ATR Spectrum of Eszopiclone.

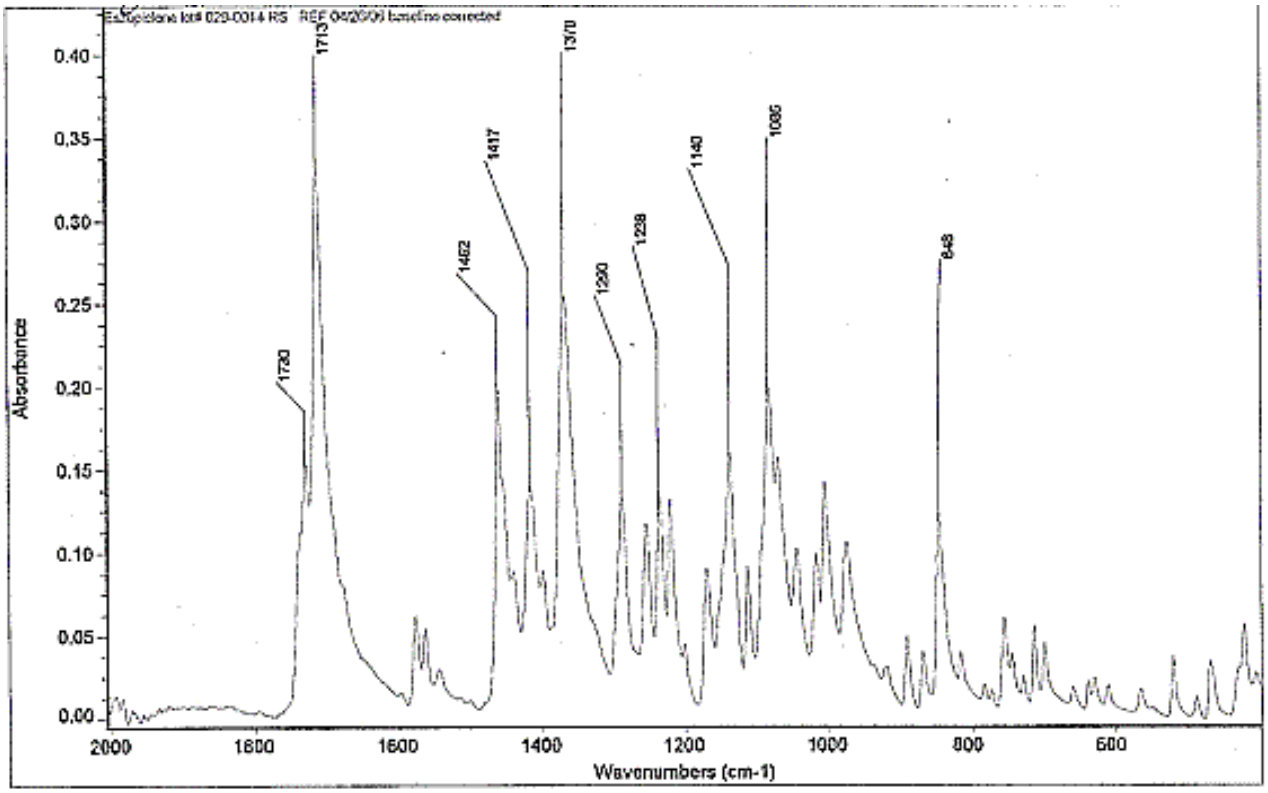

Figure 6. FTIR-ATR Spectrum of Eszopiclone, Fingerprint Region.

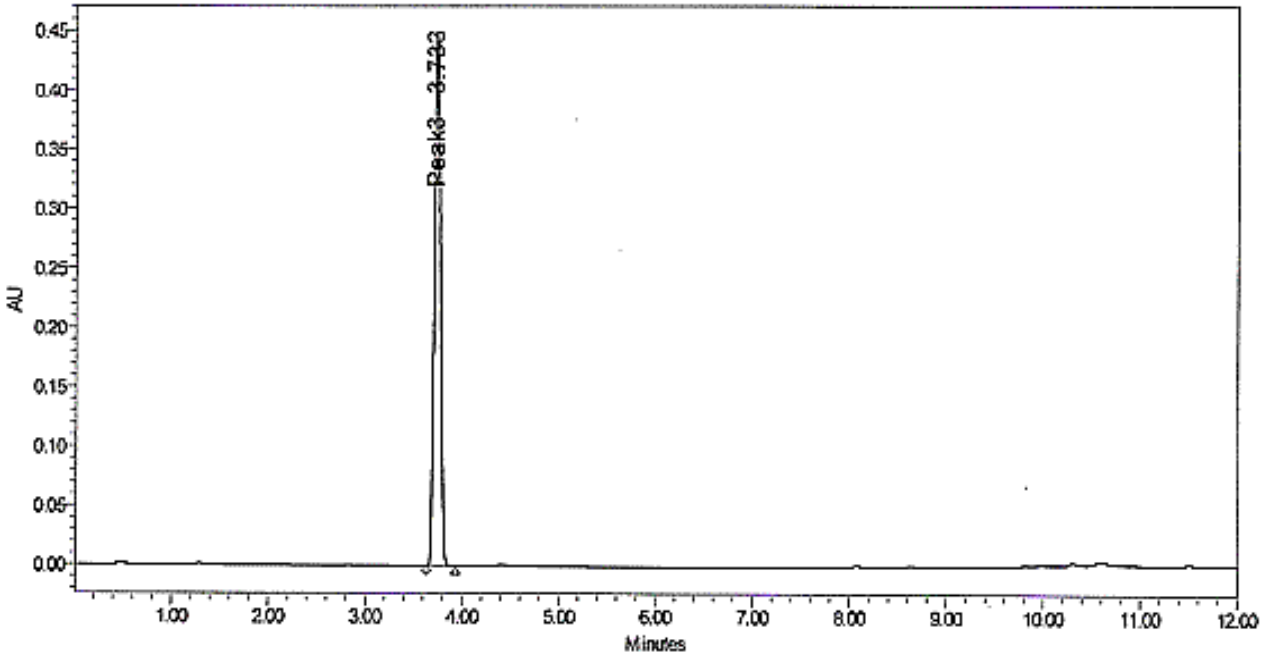

Figure 7. Ultra Performance Liquid Chromatogram of Eszopiclone.

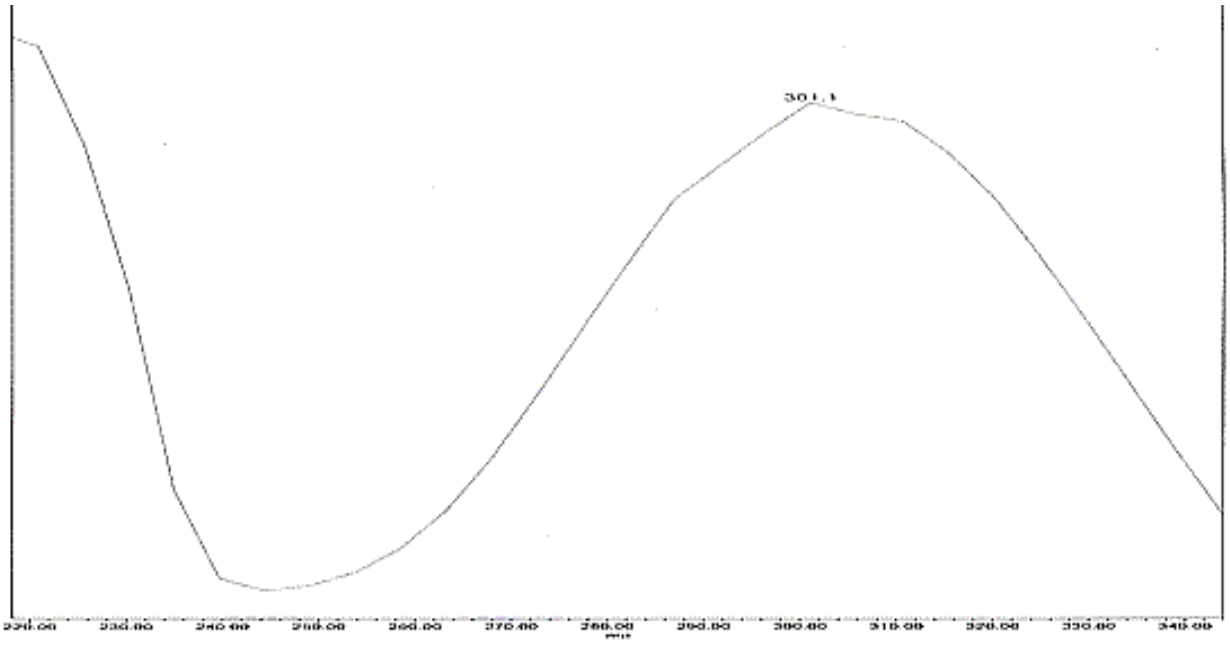

Figure 8. 220 - 340 nm UV Spectrum of Eszopiclone from UPLC. UV max = 301 nm.

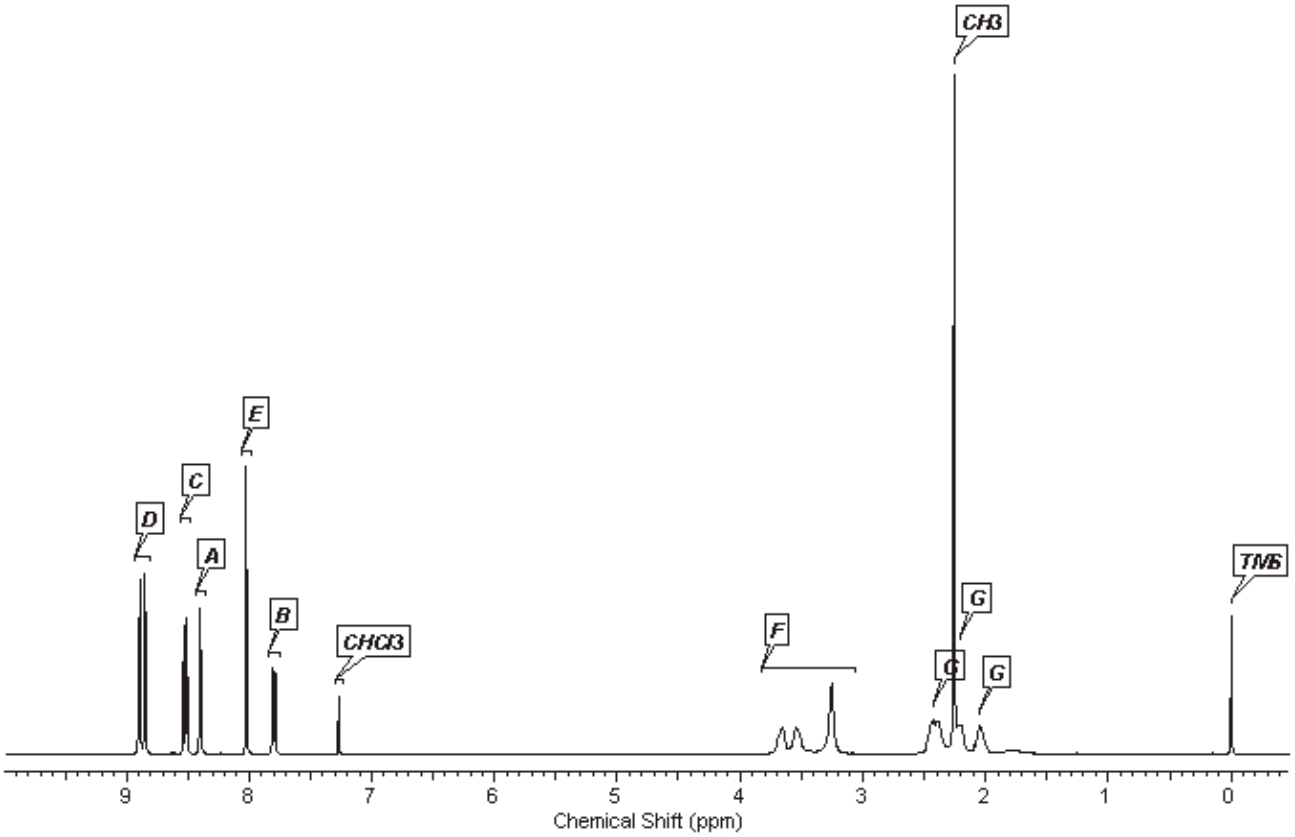

Figure 9a. 400 MHz ^{1}H-NMR Spectrum of Eszopiclone in $CDCl_3$ (See Next Page for Assignments).

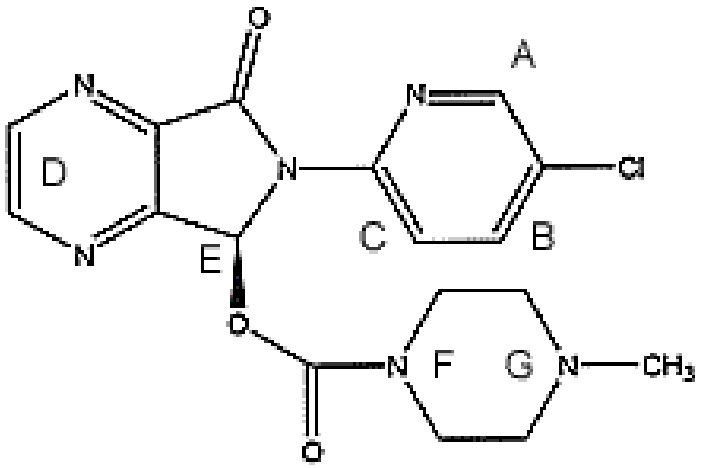

Figure 9b. Assignments of Protons for Eszopiclone (See Figure 9a for the Spectrum).

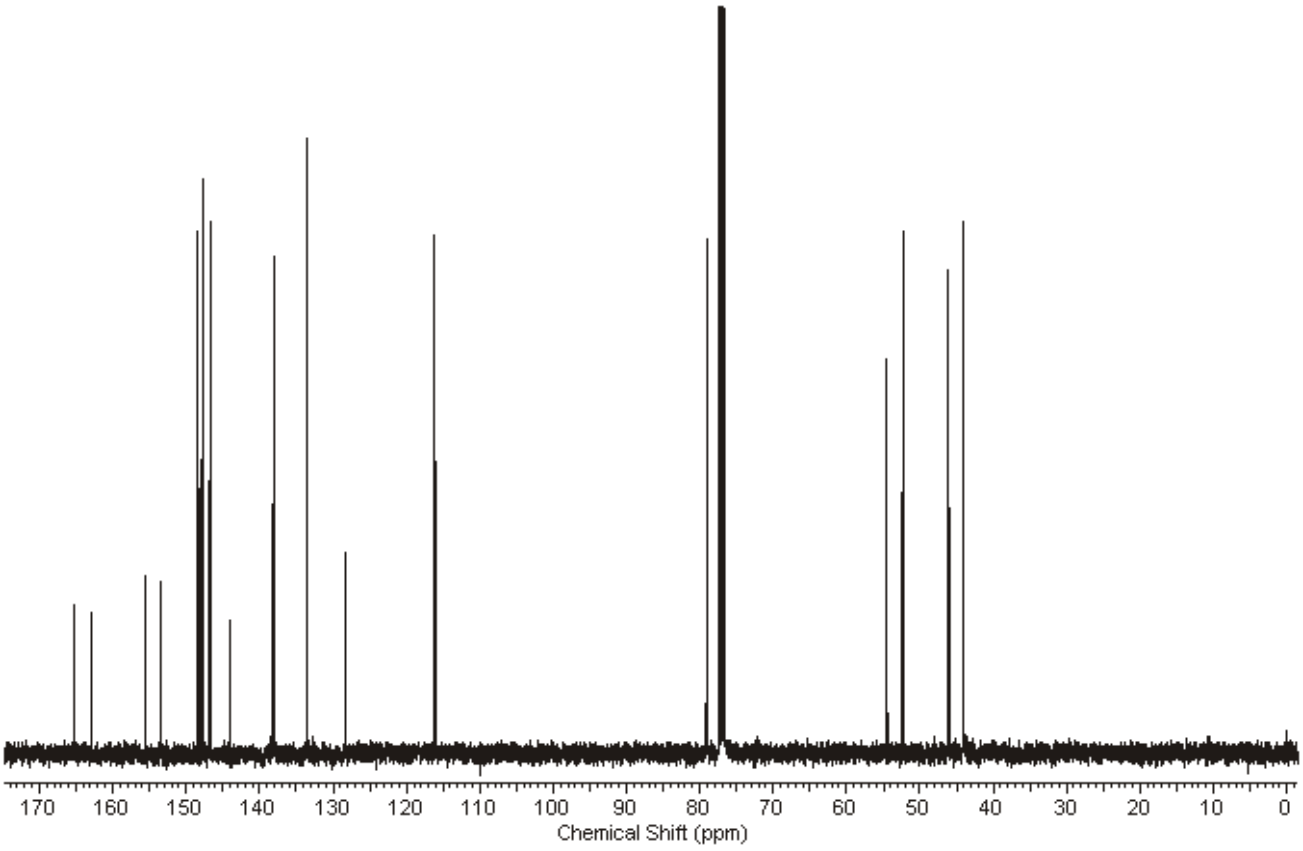

Figure 10. 100 MHz ^{13}C-NMR Spectrum of Eszopiclone in $CDCl_3$.

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