Supporting Information

A glycerol mediated domino reaction: an efficient, green synthesis of polyheterocycles incorporating a new thiochromeno[2,3-b]quinoline unit

Narsidas J. Parmar*[a], Hitesh A. Barad[a], Balvantsingh L. Labana[a], Rajnikant[b], Vivek K. Gupta[b]

[a]*Department of Chemistry, Sardar Patel University, Vallabh Vidyanagar-388120. Dist. Anand, Gujarat, India*

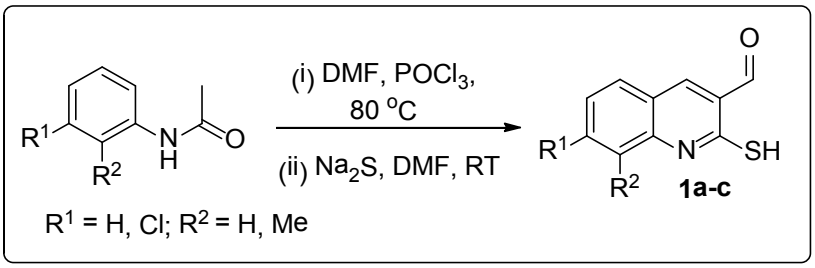
[b]*Post graduate Department of Physics, University of Jammu, Jammu Tavi-180006, India*

1.1 General methods

All solvents and reagents were used as supplied from commercial sources. The recorded melting points are uncorrected. IR spectra were recorded in KBr on Shimadzu FT-IR 8401 spectrometer and are reported in wave numbers (cm^{-1}). A single crystal-X-ray diffraction data were collected on *X'calibur* CCD area-detector diffractometer equipped with graphite monochromated MoKα radiation ((λ=0.71073 Å). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 400 spectrometer operating at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR as solutions in $CDCl_3$, unless otherwise indicated. Chemical shifts are reported as parts per million (ppm, d) and referenced to the residual protic solvent. Coupling

constants are reported in Hertz (Hz). Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; br, broad; m, multiplet; comp, complex multiplet. The degree of substitution (C, CH, CH_2, and CH_3) was determined by the APT method. The ESI mass spectra were measured on Shimadzu LCMS-2010 spectrometer. TLC was performed on Merck 60 F254 pre-coated silica plates, spots were detected either by UV (254 nm, 366 nm) or dipping into a permanganate [$KMnO_4$ (3 g), K_2CO_3 (20 g), NaOH (5 mL, 5% in H_2O), H_2O (300 mL)] or an anisaldehyde solution [3% p- methoxybenzaldehyde and 1% H_2SO_4 in MeOH] or 2,4 Dinitro phenyl hydrazine solution [2,4-DNP (12 g), Conc. H_2SO_4 (6 mL), Water (8 mL), EtOH (20 mL)] followed by heating.

1.2 General Procedure for Synthesis of 2-mercaptoquinoline-3-carbaldehydes (1a-c)



Synthesis of 2-mercaptoquinoline-3-carbaldehyde

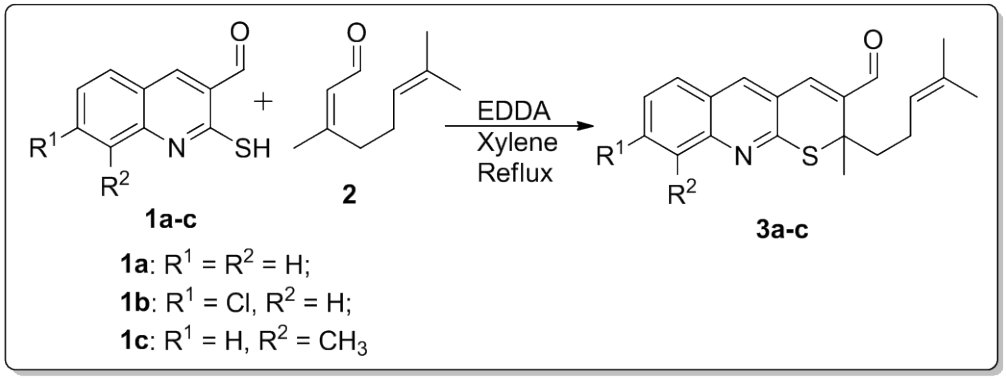
1.2.1 2-chloroquinoline-3-carbaldehyde:

$POCl_3$ (98.28 mmol) was added drop wise to DMF (34.65 mmol) while maintaining the temperature at 0–5 ˚C. The mixture was allowed to stir for about 5 min. Acetanilide (10.37 mmol) was then added and the resulting solution heated for 8 h at 75–80 ˚C. The reaction mixture was cooled to room temperature and then poured into crushed ice with stirring. A pale yellow precipitate appeared immediately and was filtered and washed with water and then dried. The crude compound was recrystallized from ethyl acetate.

1.2.2 2-mercaptoquinoline-3-carbaldehyde 1a-c :

To a solution of 2-chloroquinoline-3-carbaldehyde (1 mmole) in dry DMF (5 mL), powder sodium sulphide (1.5 mmole) was added and stirred for 1-2 h at room temperature. On completion of the reaction, the reaction mixture was poured into ice-water and made acidic with acetic acid. The product was filtered off, washed well with water, dried and was pure enough for further use.

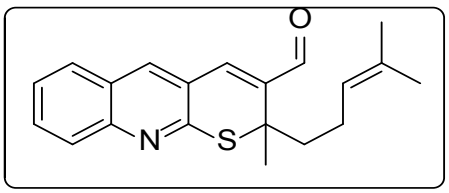
1.3 General Experimental Procedure and anaylitical data for Synthesis of thiopyrano[2,3-*b*]quinoline-3-carbaldehydes (3a-c)



Synthesis of thiopyrano[2,3-*b*]quinoline-3-carbaldehydes **3a-c**

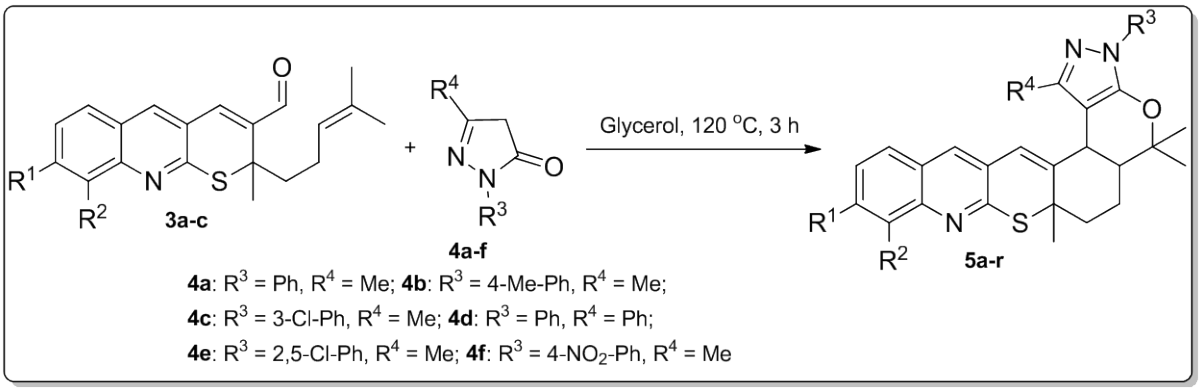
2-mercaptoquinoline-3-carbaldehyde (**1a-c**) (2.0 mmol) and citral (**2**) (2.4 mmol) were dissolved in xylene (20 mL), and ethylenediamine diacetate (0.4 mmol) was added at room temperature. The mixture was refluxed for 3-3.5 h and then cooled to room temperature. Removal of solvent at reduced pressure left an oily residue, which was then purified by column chromatography on silica gel using a mixture of hexane/ethyl acetate (10 : 1) as an eluent to give product **3a-c** as a yellow solid.

2-methyl-2-(4-methylpent-3-en-1-yl)-2H-thiopyrano[2,3-*b*]quinoline-3-carbaldehyde (3a):



Isolated Yield (0.46 g, 72 %) as yellow crystals, mp 70-72 °C; ν_{max}/cm^{-1} = 3054.20, 2973.43, 2900.84, 2852.91, 1683.90, 1608.90, 1553.70, 1374.75, 1177.35, 1094.67, 920.27, 741.27; δ_H (400 MHz, $CDCl_3$) 1.53 (s, 3H, CH_3), 1.63 (s, 3H, CH_3), 1.69-1.79 (m, 2H, CH_2), 1.83 (s, 3H, C(2)CH_3), 1.96-2.28 (m, 2H, CH_2), 2.35 (s, 1H, C(4)H), 5.04 (t, 1H, J = 6.8 Hz, CH), 7.45-7.95 (m, 5H, Ar-H), 9.63 (s, 1H, C<u>H</u>O) ppm; δ_C (100 MHz; $CDCl_3$) 24.46, 25.55, 29.19, 41.86, 51.33, 123.18, 123.73, 126.26, 128.05, 128.55, 131.56, 136.82, 137.01, 141.33, 145.46, 145.76, 149.28, 158.74, 191.33 ppm; m/z (ESI) 323.9 [M + H^+].

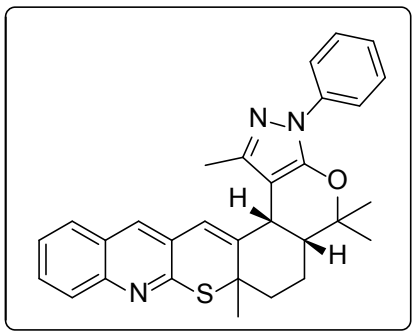
1.4 General experimental procedure for synthesis of pyrazolo[4'',3'':5',6'] pyrano[4',3':5,6] thiochromeno[2,3-b]quinolines (5a-r)



Some 3 mL glycerol were added to an equimolar (3 mmol of each) mixture containing thiopyrano[2,3-*b*]quinoline-3-carbaldehyde (**3a-c**) and 5-pyrazolone (**4a-f**) taken in a 50 mL round-bottomed flask connected to a reflux condenser. The mixture was then stirred at 120 °C. The progress of reaction was monitored by TLC using EtOAc–n-hexane (1:4) as an eluent. After completion of the reaction, 5 mL warm water was added to flask. Insoluble crude products thus precipitated were isolated simply by filtration. The filtrate upon water evaporation under reduced pressure at 100 °C left glycerol. The recovered glycerol was reused for the preparation of next product. All the compounds **5a-r** were received quantitatively with an excellent purity.

1.5 Analytical data for compounds

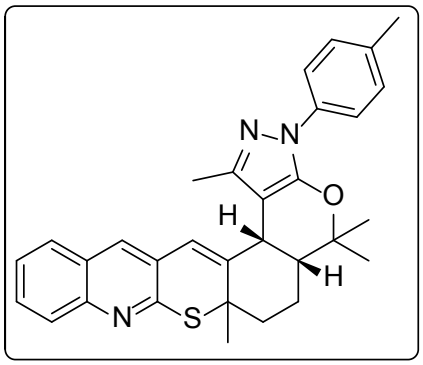
(5a*R*,15b*S*)1,5,5,7a-tetramethyl-3-phenyl-5,5a,6,7,7a,15b-hexahydro-3*H*-pyrazolo[4'',3'':5',6']pyrano[4',3':5,6] thiochromeno[2,3-*b*]quinoline (5a)



Isolated Yield (1.30 g, 91 %) as yellow crystals, mp 260-262 °C; ν_{max}/cm^{-1} = 3059.33, 2979.50, 2946.72, 2917.59, 1648.57, 1598.74, 1510.21, 1390.82, 1119.83, 749.23, 689.78; δ_H (400 MHz, $CDCl_3$) 1.28 (s, 3H, C(5)CH_3), 1.50 (s, 3H, C(5)CH_3), 1.64 (s, 3H, C(7a)H), 1.99-2.10 (m, 4H, C(6)&C(7)CH_2), 2.30 (s, 4H, C(1)CH_3), 2.40-2.47 (m, 1H, C(5a)H), 3.70 (d, 1H, J = 8.4 Hz, C(15b)H), 6.40 (s, 1H, C(15)H), 7.22-7.97 (m, 10H, Ar-H) ppm; δ_C (100 MHz; $CDCl_3$) 13.28, 21.07, 22.08, 28.13, 30.25, 30.86, 31.91, 33.49, 41.02, 48.01, 84.58, 93.99,

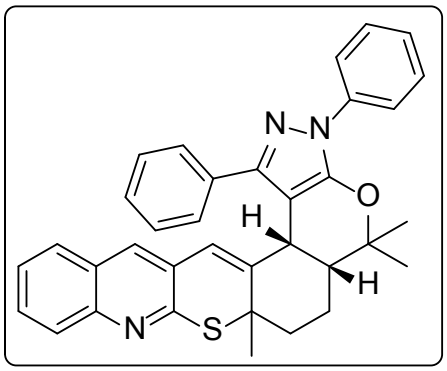
120.10, 122.17, 125.33, 125.83, 126.43, 126.76, 127.63, z127.77, 128.85, 129.59, 132.61, 138.92, 143.27, 147.19, 147.34, 150.46, 158.08 ppm; m/z (ESI) 479.7 [M + H^+].

(5a*R*,15b*S*)1,5,5,7a-tetramethyl-3-(p-tolyl)-5,5a,6,7,7a,15b-hexahydro-3*H*-pyrazolo[4'',3'':5',6']pyrano[4',3':5,6]thiochromeno[2,3-*b*]quinoline (5b):



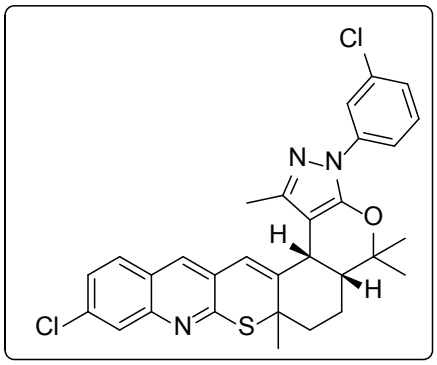
Isolated Yield (1.4 g, 90 %) as yellow crystals, mp 228-230 °C; ν_{max}/cm^{-1} = 3034.40, 2921.48, 1605.22, 1581.97, 1517.87, 1391.67, 1100.35, 818.66, 749.54; δ_H (400 MHz, $CDCl_3$) 1.27 (s, 3H, C(5)CH_3), 1.48 (s, 3H, C(5)CH_3), 1.64 (s, 3H, C(7a)H), 1.82-2.07 (m, 4H, C(6) & C(7)CH_2), 2.29 (s, 3H, C(1)CH_3), 2.39 (s, 3H, *p*-CH_3), 2.41-2.44 (m, 1H, C(5a)H), 3.70 (d, 1H, *J* = 8.4 Hz, C(15b)H), 6.40 (s, 1H, C(15)H), 7.23-7.96 (m, 9H, C(Ar)H) ppm; δ_C (100 MHz; $CDCl_3$) 13.35, 20.71, 20.94, 22.13, 28.31, 30.29, 31.96, 33.57, 41.13, 41.35, 47.99, 69.80, 84.26, 120.28, 122.17, 125.87, 126.45, 126.80, 127.57, 129.50, 132.21, 132.49, 135.05, 136.47, 143.25, 143.97, 147.02ppm; m/z (ESI) 493.9 [M + H^+].

(5a*R*,15b*S*)5,5,7a-trimethyl-1,3-diphenyl-5,5a,6,7,7a,15b-hexahydro-3*H*-pyrazolo[4'',3'':5',6']pyrano[4',3':5,6]thiochromeno[2,3-*b*]quinoline (5d)



Isolated Yield (1.5 g, 91 %) as yellow crystals, mp 234-236 °C; ν_{max}/cm^{-1} = 3052.94, 2931.77, 3856.28, 1596.64, 1509.94, 1484.66, 1386.03, 1136.04, 1070.22, 752.18, 691.55; δ_H (400 MHz, $CDCl_3$) 1.32 (s, 3H, C(5)CH_3), 1.53 (s, 3H, C(5)CH_3), 1.68 (s, 3H, C(7a)H), 1.88-2.17 (m, 4H, C(6) & C(7)CH_2), 2.52-2.59 (m, 1H, C(5a)H), 4.09 (d, 1H, *J* = 8.4 Hz, C(15b)H), 6.30 (s, 1H, C(15)H), 7.31-7.99 (m, 15H, Ar-H) ppm; δ_C (100 MHz; $CDCl_3$) 13.33, 20.76, 22.06, 28.31, 30.32, 31.88, 33.49, 41.05, 48.07, 84.98, 117.71, 119.99, 121.98, 125.12, 125.19, 126.49, 126.87, 127.02, 128.70, 129.96, 132.10, 134.71, 135.37, 143.49, 147.54, 147.89, 159.48 ppm.

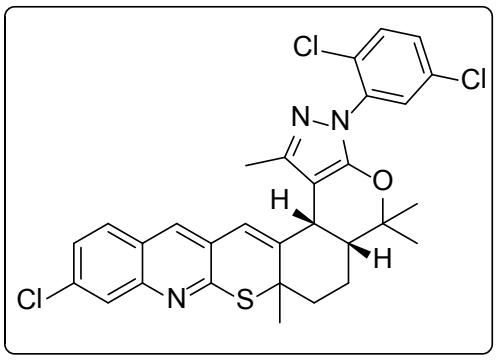
(5a*R*,15b*S*) 11-chloro-3-(3-chlorophenyl)-1,5,5,7a-tetramethyl-5,5a,6,7,7a,15b-hexahydro-3*H*-pyrazolo[4'',3'':5',6']pyrano[4',3':5,6]thiochromeno[2,3-*b*]quinoline (5i)



Isolated Yield (1.4 g, 90 %) as yellow crystals, mp 170-172 ˚C; ν_{max}/cm^{-1} = 3071.39, 2929.44, 2856.39, 1607.66, 1593.91, 1505.63, 1478.33, 1387.09, 1119.11, 1078.51, 927.51, 881.80, 774.60, 751.77; δ_H (400 MHz, $CDCl_3$) 1.27 (s, 3H, C(5)CH_3), 1.51 (s, 3H, C(5)CH_3), 1.63 (s, 3H, C(7a)H), 1.81-2.11 (m, 4H, C(6) & C(7)CH_2), 2.28 (s, 3H, C(1) CH_3), 2.40-2.47 (m, 1H, C(5a)H), 3.69 (d, 1H, J = 6.8 Hz, C(15b)H), 6.35 (s, 1H, C(15)H), 7.19-7.94 (m, 8H, Ar-H) ppm; δ_C (100 MHz; $CDCl_3$) 13.33, 20.76, 22.06, 28.31, 30.32, 31.88, 33.49, 41.05, 48.07, 84.98, 117.71, 119.99, 121.98, 125.12, 125.19, 126.49, 126.87, 127.02, 128.70, 129.96, 132.10, 134.71, 135.37, 143.49, 147.54, 147.89, 159.48 ppm; m/z (ESI) 547.9 [M + H^+].

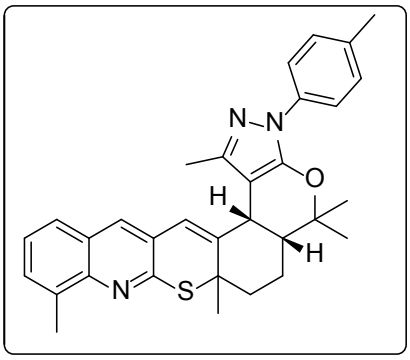
(5a*R*,15b*S*) 11-chloro-3-(2,5-dichlorophenyl)-1,5,5,7a-tetramethyl-5,5a,6,7,7a,15b-hexahydro-3*H*-pyrazolo[4'',3'':5',6']pyrano[4',3':5,6]thiochromeno[2,3-*b*]quinoline (5k):

Isolated Yield (1.5 g, 90 %) as yellow crystals, mp 138-140 ˚C; ν_{max}/cm^{-1} = 3070.95,



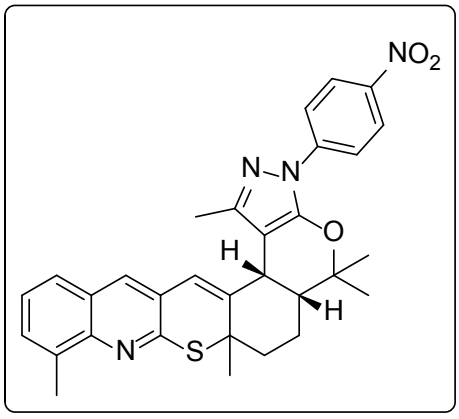
2923.80, 2858.22, 1605.67, 1512.87, 1476.11, 1138.50, 1092.57, 927.73, 870.76, 806.87, 771.99, 656.08, 581.54; δ_H (400 MHz, $CDCl_3$) 1.26 (s, 3H, C(5)CH_3), 1.38 (s, 3H, C(5)CH_3), 1.63 (s, 3H, C(7a)H), 1.81-2.11 (m, 4H, C(6) & C(7) CH_2), 2.28 (s, 3H, C(1)CH_3), 2.38-2.43 (m, 1H, C(5a)H), 3.70 (d, 1H, J = 8.4 Hz, C(15b)H), 6.38 (s, 1H, C(15)H), 7.33-7.95 (m, 7H, Ar-H) ppm; δ_C (100 MHz; $CDCl_3$) 13.44, 20.27, 22.10, 28.33, 30.55, 31.90, 33.57, 40.95, 48.12, 85.02, 117.88, 120.09, 122.08, 125.27, 125.37, 126.65, 126.98, 127.92, 128.70, 130.12, 132.08, 135.55, 143.65, 147.78, 147.98, 160.04 ppm.

(5a*R*,15b*S*) 1,5,5,7a,10-pentamethyl-3-(p-tolyl)-5,5a,6,7,7a,15b-hexahydro-3*H*-pyrazolo[4'',3'':5',6']pyrano[4',3':5,6]thiochromeno[2,3-*b*]quinoline (5n):



Isolated Yield (1.3 g, 89 %) as yellow crystals, mp 236-238 ˚C; ν_{max}/cm^{-1} = 3033.95, 2950.81, 2920.92, 1608.16, 1515.93, 1390.42, 1327.19, 1105.03, 817.96, 756.88; δ_H (400 MHz, $CDCl_3$) 1.26 (s, 3H, C(5)CH_3), 1.48 (s, 3H, C(5)CH_3), 1.64 (s, 3H, C(7a)H), 1.98-2.03 (m, 4H, C(6) & C(7)CH_2), 2.29 (s, 3H, C(1)CH_3), 2.33 (s, 3H, C(4^1)CH_3), 2.40 (m, 1H, C(5a)H), 2.77 (s, 3H, C(10)CH_3), 3.70 (d, 1H, J = 8.4 Hz, C(15b)H), 6.39 (s, 1H, C(15)H), 7.25-7.79 (m, 8H, C(Ar)H)ppm; δ_C (100 MHz; $CDCl_3$) 12.88, 13.31, 17.89, 20.68, 20.95, 21.05, 22.09, 28.29, 30.24, 31.85, 33.58, 41.13, 47.87, 84.43, 93.82, 120.31, 121.10, 122.23, 125.58, 126.11, 126.72, 129.43, 129.46, 129.72, 132.88, 135.08, 135.86, 138.17, 142.76, 146.54, 147.09, 156.76 ppm.

(5a*R*,15b*S*) 1,5,5,7a,10-pentamethyl-3-(4-nitrophenyl)-5,5a,6,7,7a,15b-hexahydro-3*H*-pyrazolo[4'',3'':5',6']pyrano[4',3':5,6]thiochromeno[2,3-*b*]quinoline (5r):



Isolated Yield (1.4 g, 86 %) as yellow crystals, mp 248-250 ˚C; ν_{max}/cm^{-1} = 3119.95, 2947.44, 2917.86, 1595.17, 1511.41, 1392.17, 1336.60, 1106.03, 851.67, 750.97, 511.18; δ_H (400 MHz, $CDCl_3$) 1.29 (s, 3H, C(5)CH_3), 1.57(s, 3H, C(5)CH_3), 1.65 (s, 3H, C(7a)H), 2.01-2.06 (m, 4H, C(6) & C(7)CH_2), 2.31 (s, 3H, C(1)CH_3), 2.40-2.45 (m, 1H, C(5a)H), 2.77 (s, 3H, C(10)CH_3), 3.71 (d, 1H, J = 7.2 Hz, C(15b)H), 6.34 (s, 1H, C(15)H), 7.28-8.32 (m, 8H, Ar-H) ppm; δ_C (100 MHz; $CDCl_3$) 13.41, 17.87, 19.10, 20.85, 22.05, 23.33, 28.38, 30.22, 31.81, 33.54, 40.95, 47.78, 48.96, 85.81, 95.49, 117.68, 118.79, 122.39, 124.76, 125.01, 125.71, 125.87, 126.68, 132.90, 135.91, 142.16, 143.97, 146.31, 149.68 ppm; m/z (ESI) 538.7 [M + H^+].

1.6 Single crystal X-Ray data

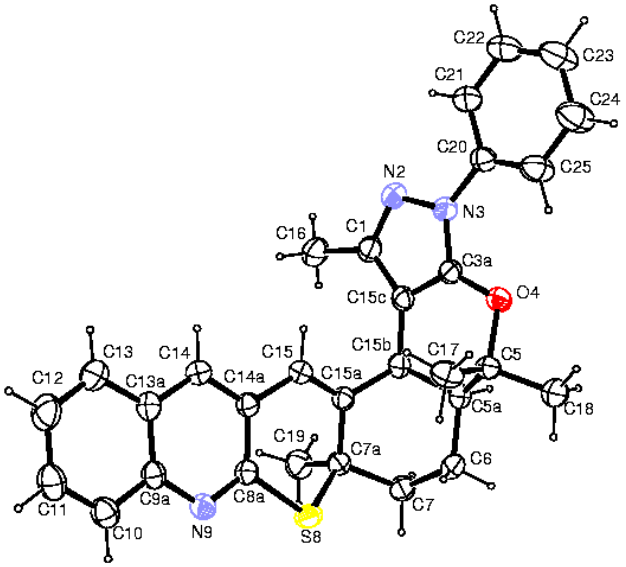


Figure 3: *ORTEP* view of the molecule **5a.**

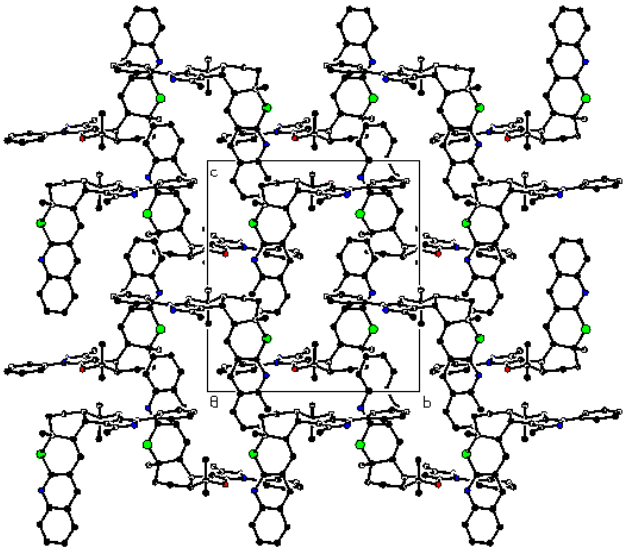


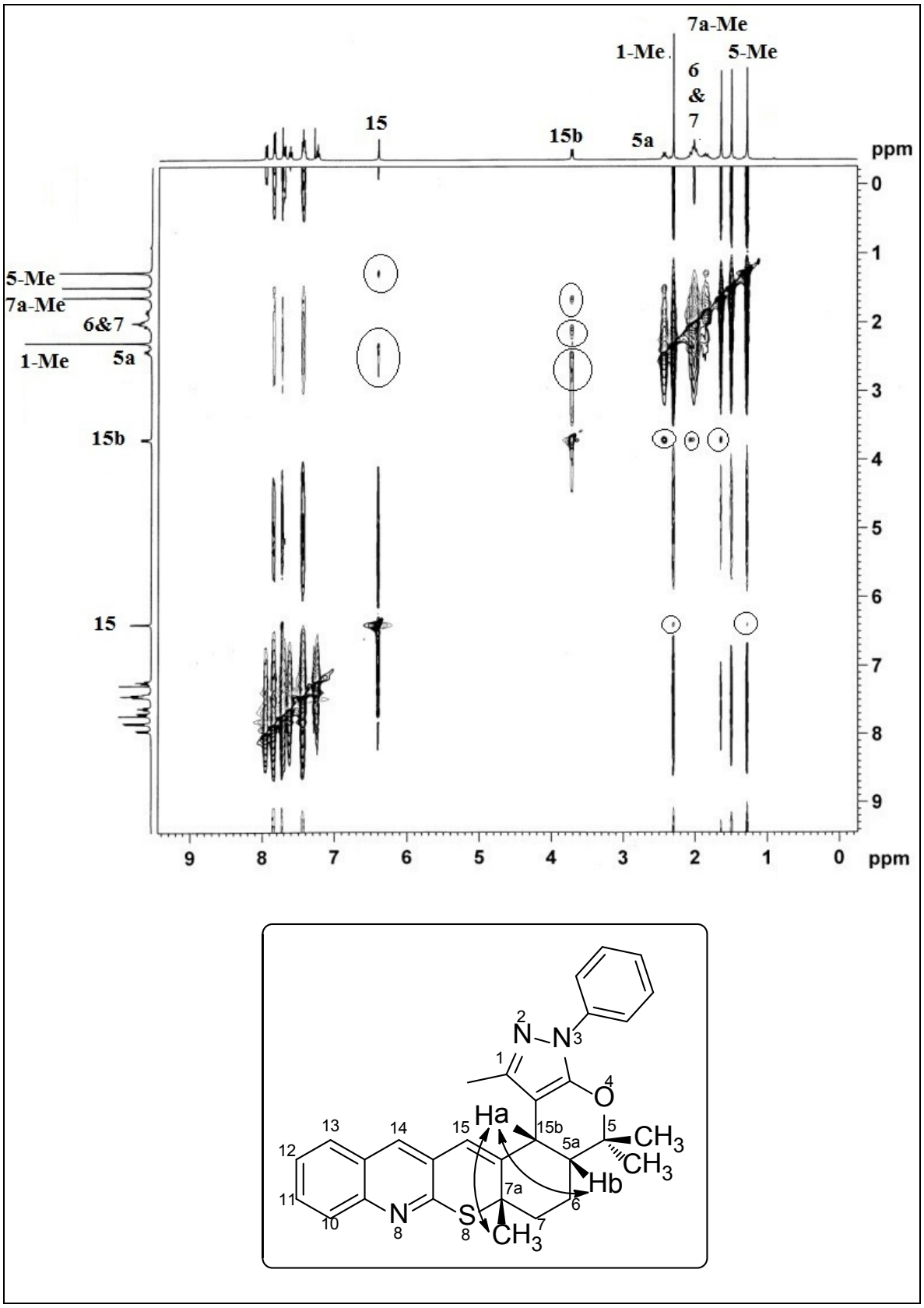
Figure 4: The packing arrangement of molecules **5a**

Table 1 Crystal and experimental data of 5a

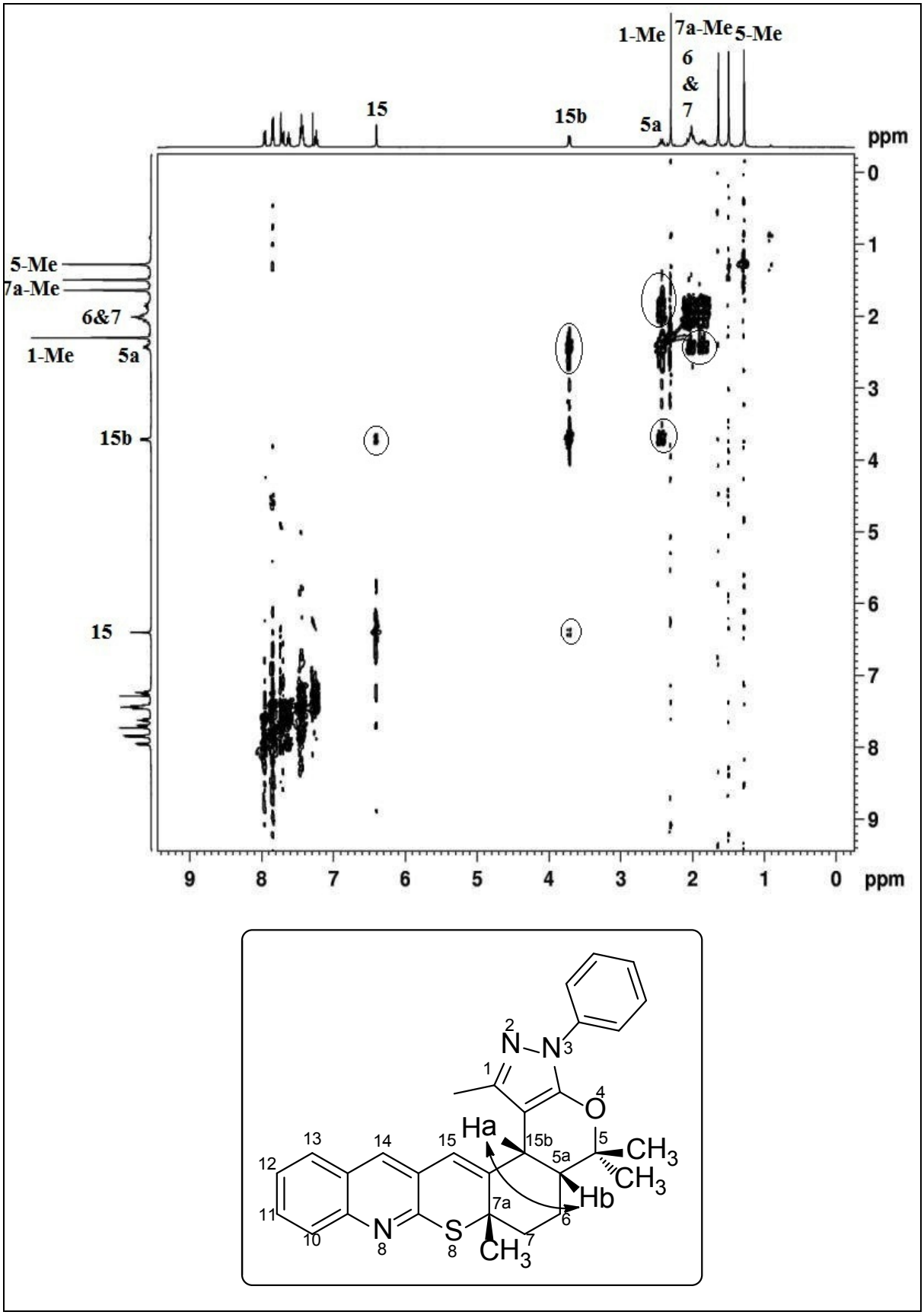
CCDC No	914747
Crystal description	yellow block
Crystal size	0.30 x 0.20 x 0.20 mm
Empirical formula	$C_{30}\ H_{29}N_3OS$
Formula weight	479.62
Radiation, Wavelength	Mo *K*α, 0.71073 Å
Unit cell dimensions	a=10.3294(2), b= 14.8602(4), c=19.1562(4) Å, β=122.631(1) º
Crystal system	Monoclinic
Space group	P $2_1/c$
Unit cell volume	2476.30(10) $Å^3$
No. of molecules per unit cell, Z	4
Absorption coefficient(μ)	0.159 mm^{-1}
F (000)	1016
θ range for entire data collection	$3.38 < \theta < 26.00$
Reflections collected / unique	74367 / 4863
Reflections observed [$I > 2\sigma(I)$]	3823
No. of parameters refined	320
Final R	0.0436
wR(F^2)	0.0979
Goodness-of-fit	1.040
$(\Delta/\sigma)_{max}$ in the final cycle	0.001
Final residual electron density	$-0.227 < \Delta\rho < 0.222$ $eÅ^{-3}$

1.7 2D NMR experiments: NOE and Cosy for 5a

NOE for 5a

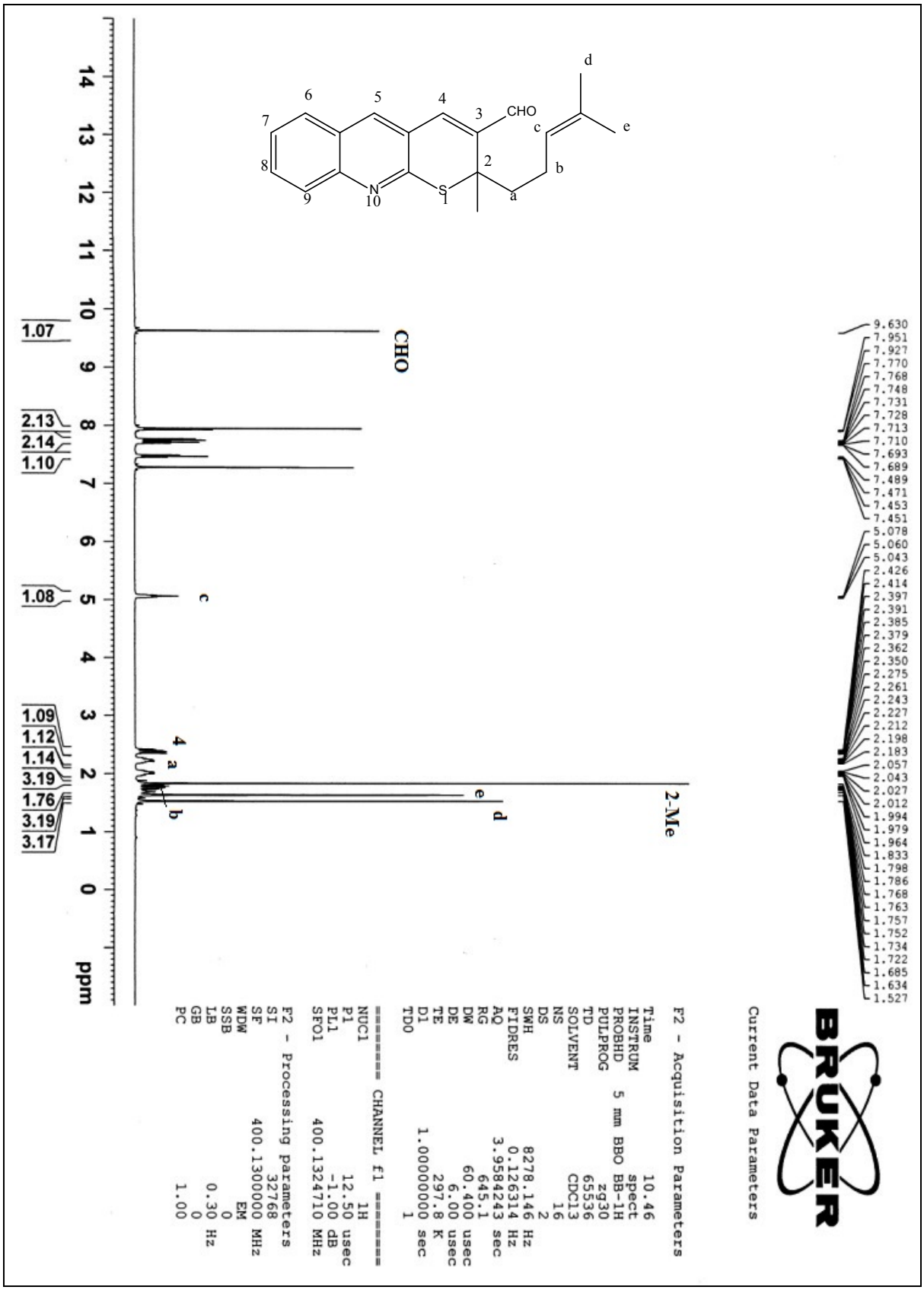


Cosy for 5a

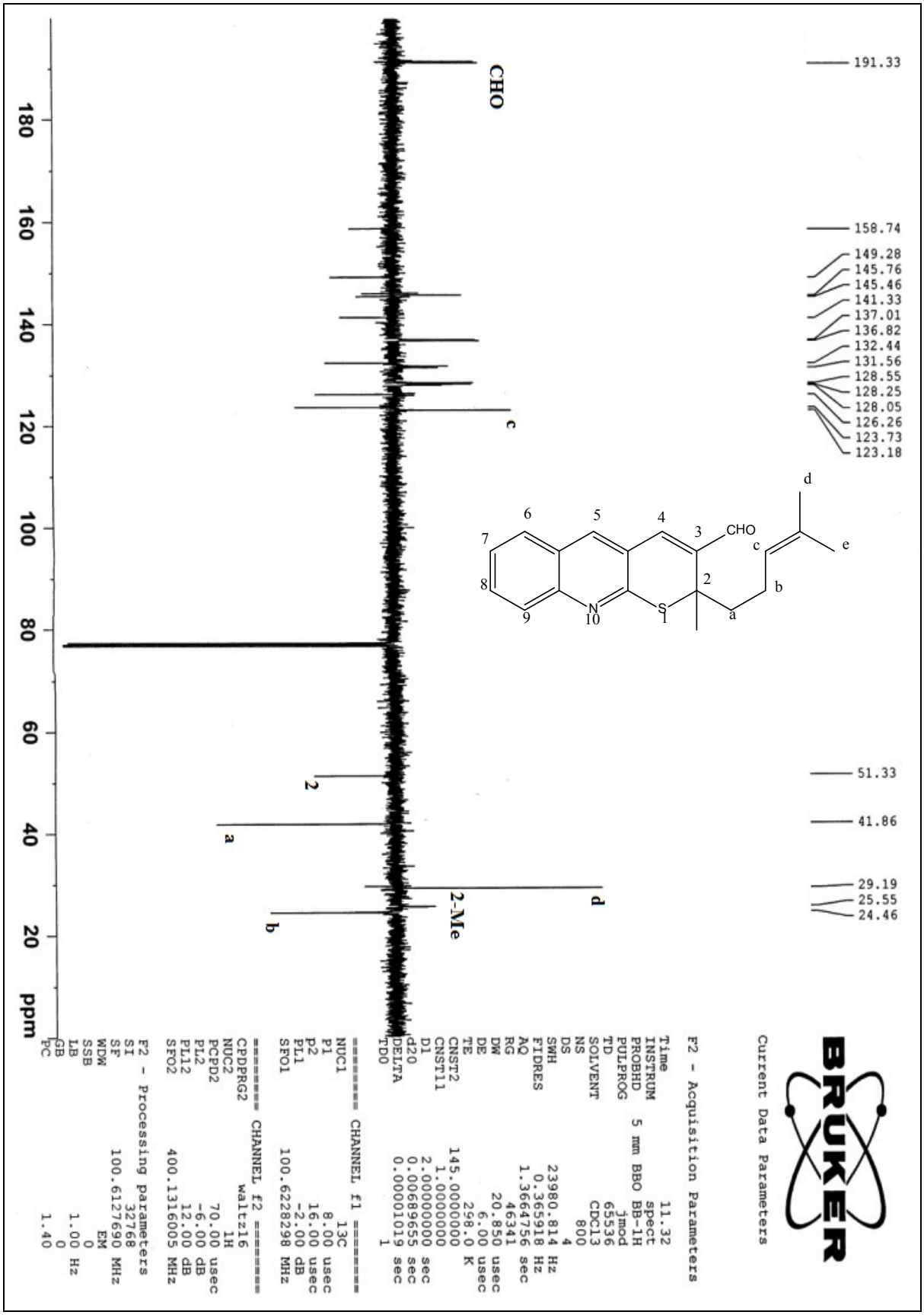

1-Me
7a-Me
5-Me
6
&
7
15
15b
5a
ppm
5-Me
7a-Me
6&7
1-Me
5a
15b
15
9
8
7
6
5
4
3
2
1
0
ppm
N
N
O
Ha
Hb
CH3
CH3
CH3
S
N

1.8 ^{1}H NMR, ^{13}C NMR, Mass and IR Spectral Data

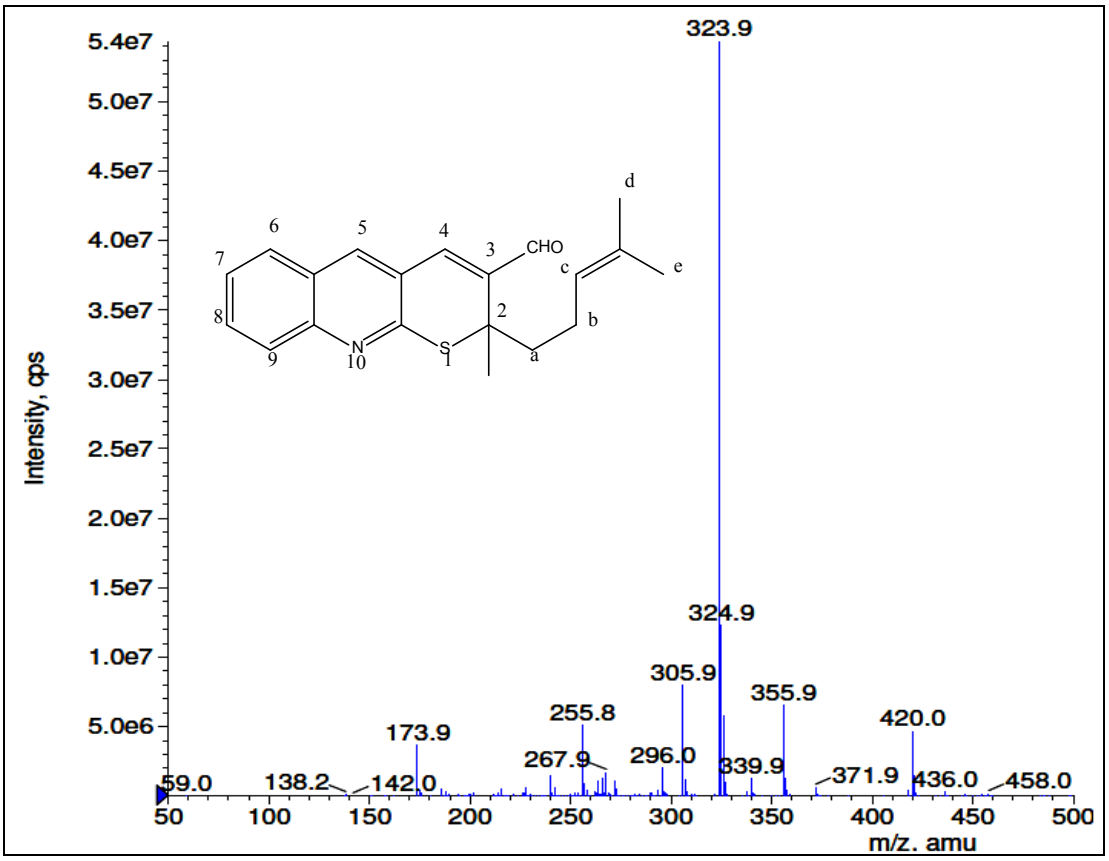
^{1}H NMR spectrum of compo und 3a



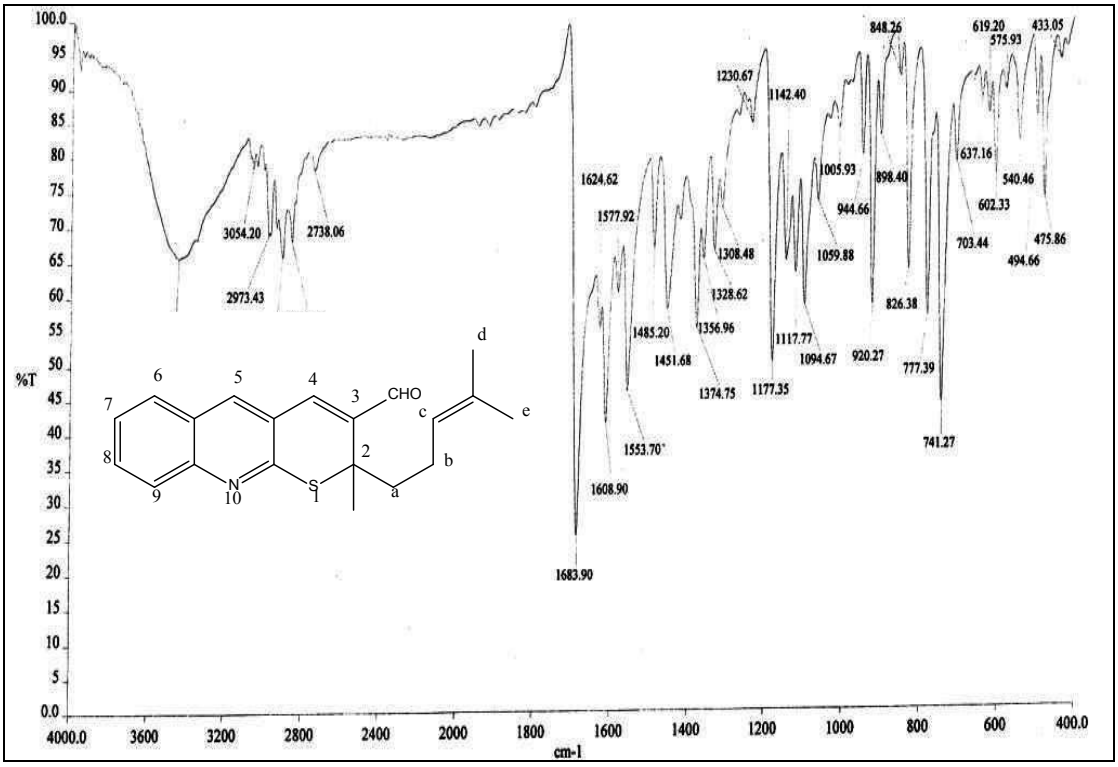
APT spectrum of compound 3a



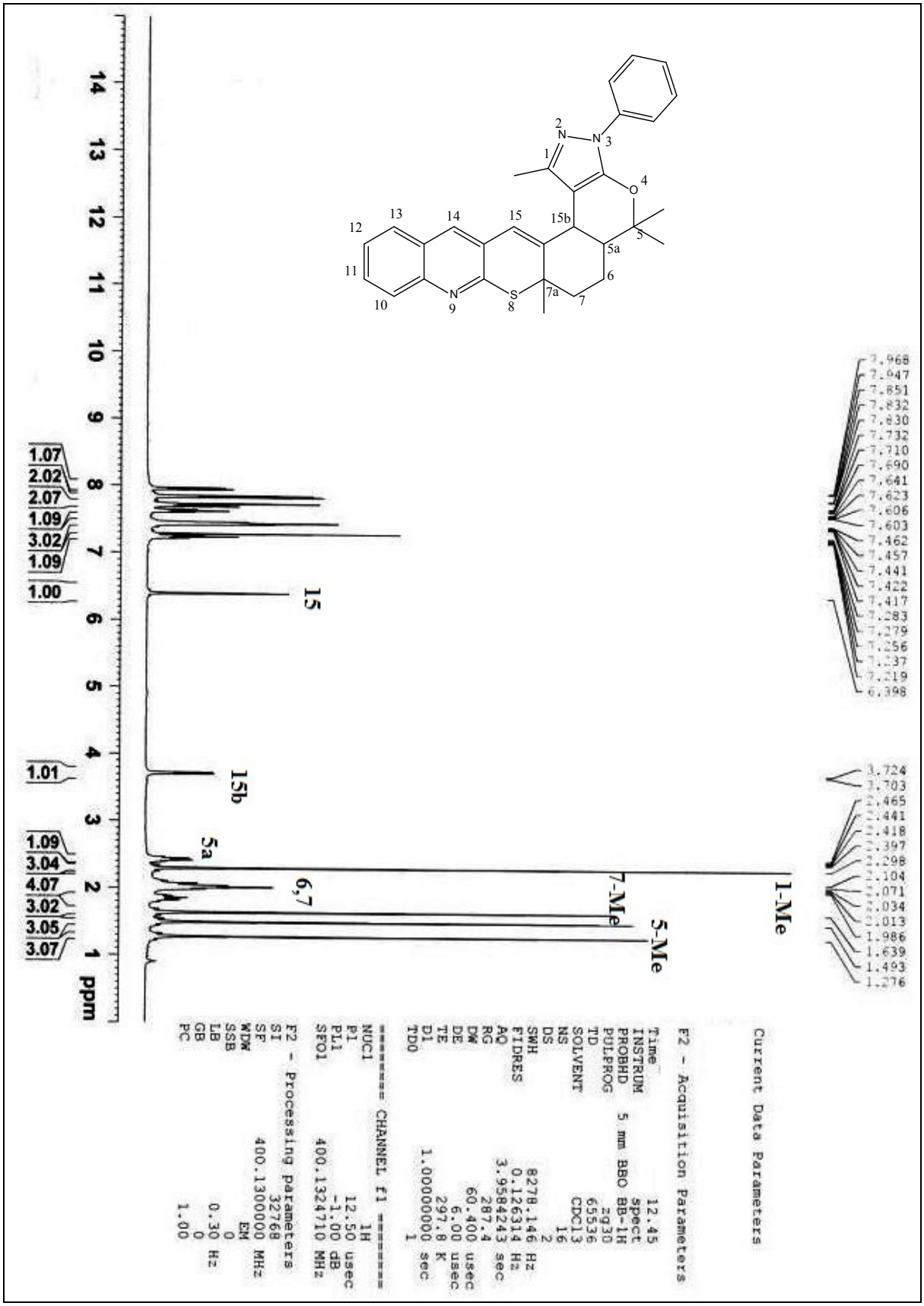
ESI-MS of compound 3a



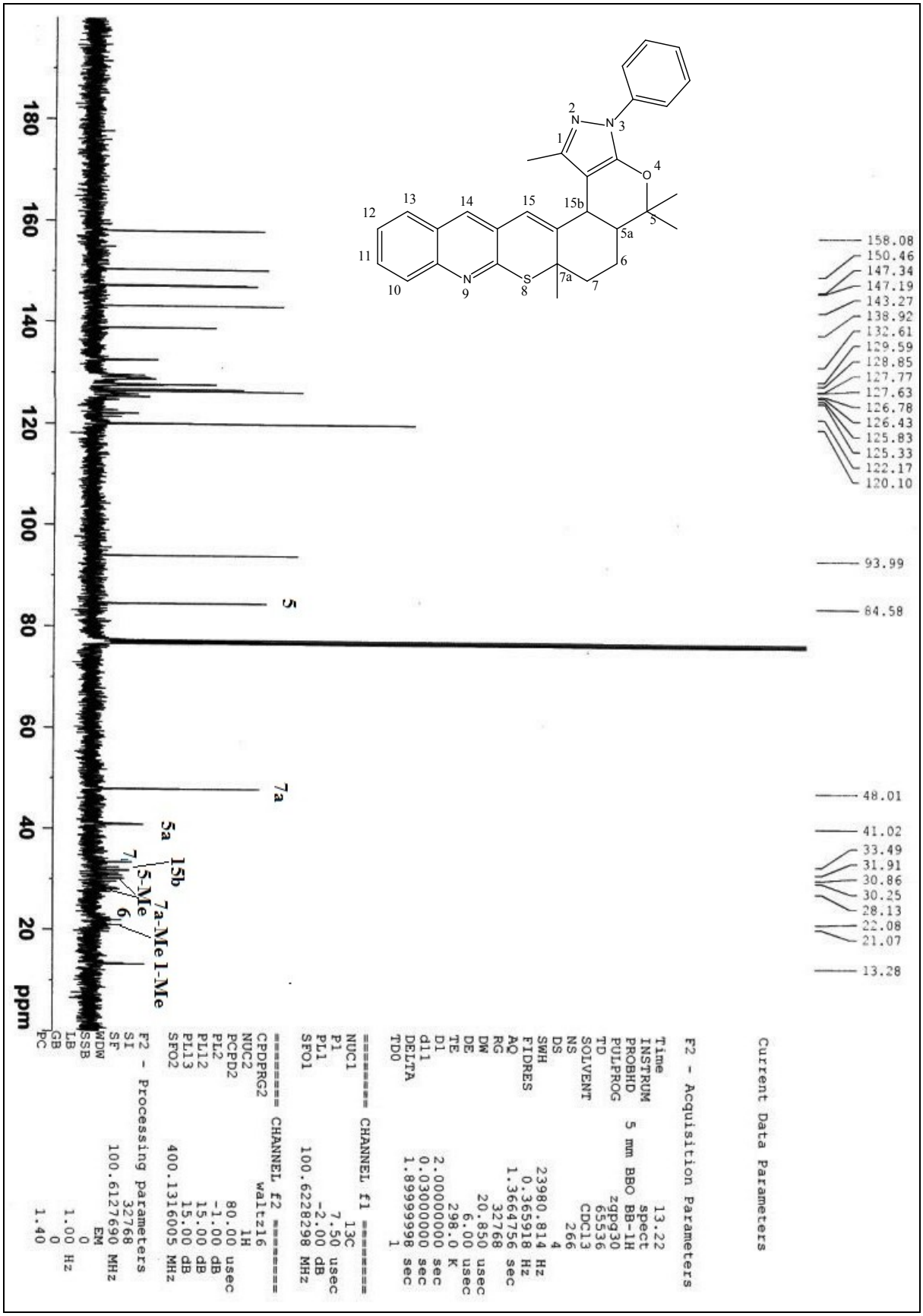
FT-IR spectrum of compound 3a



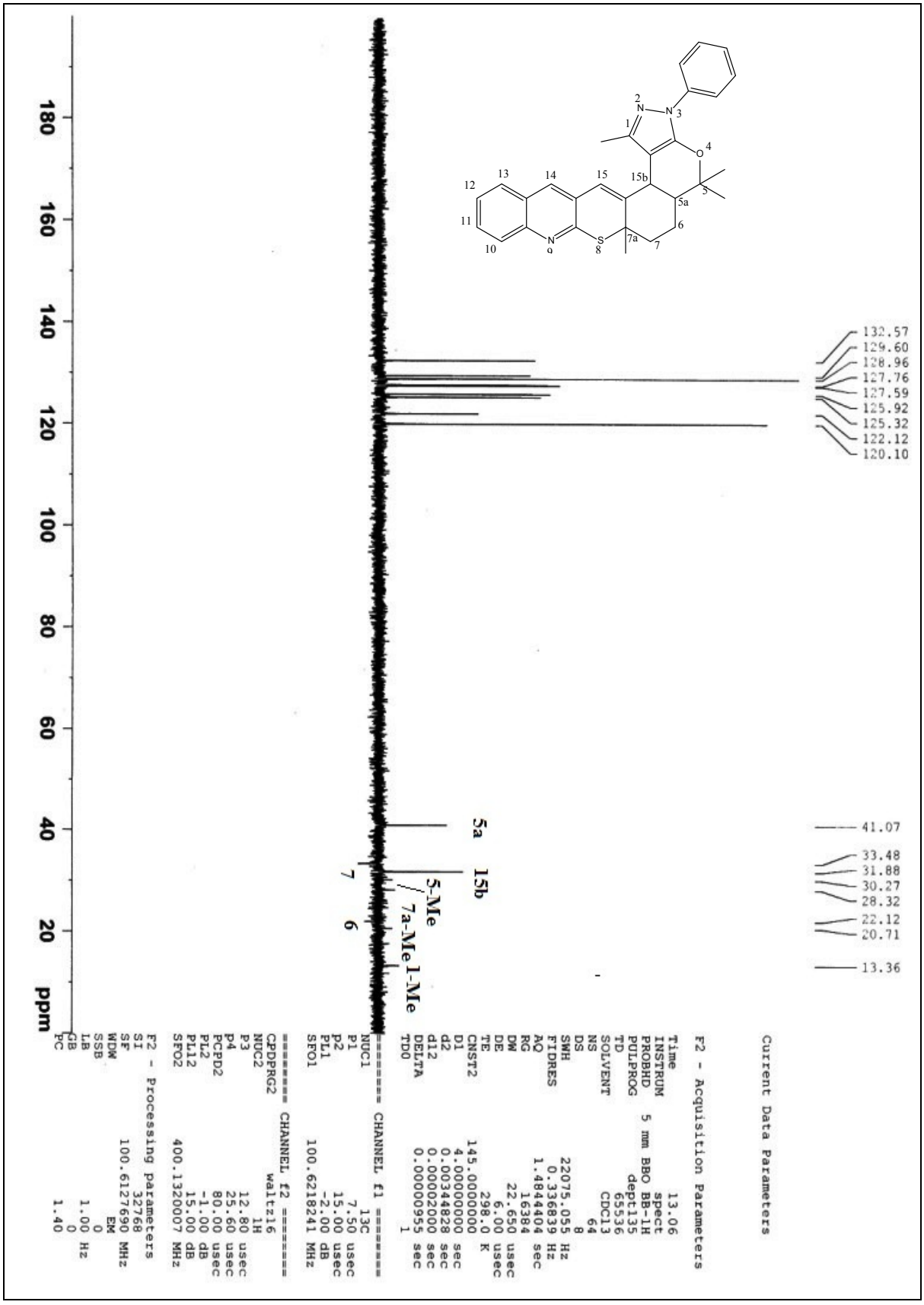
^{1}H NMR spectrum of compound 5a



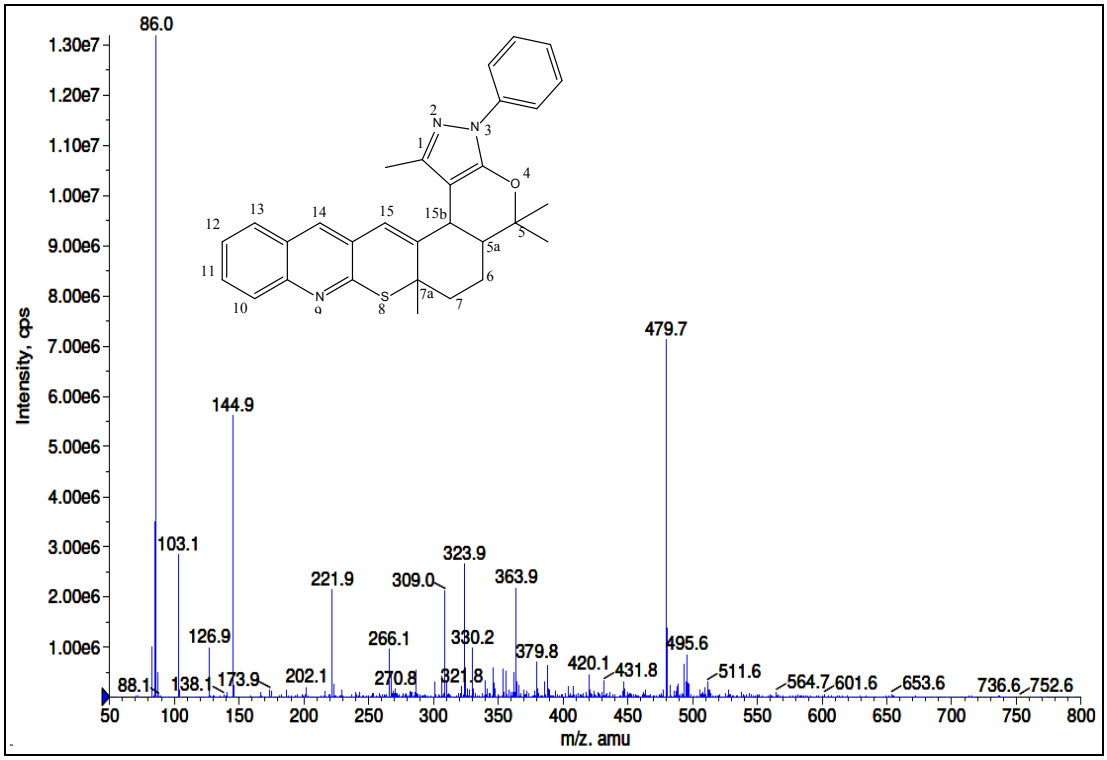
^{13}C NMR spectrum of compound 5a



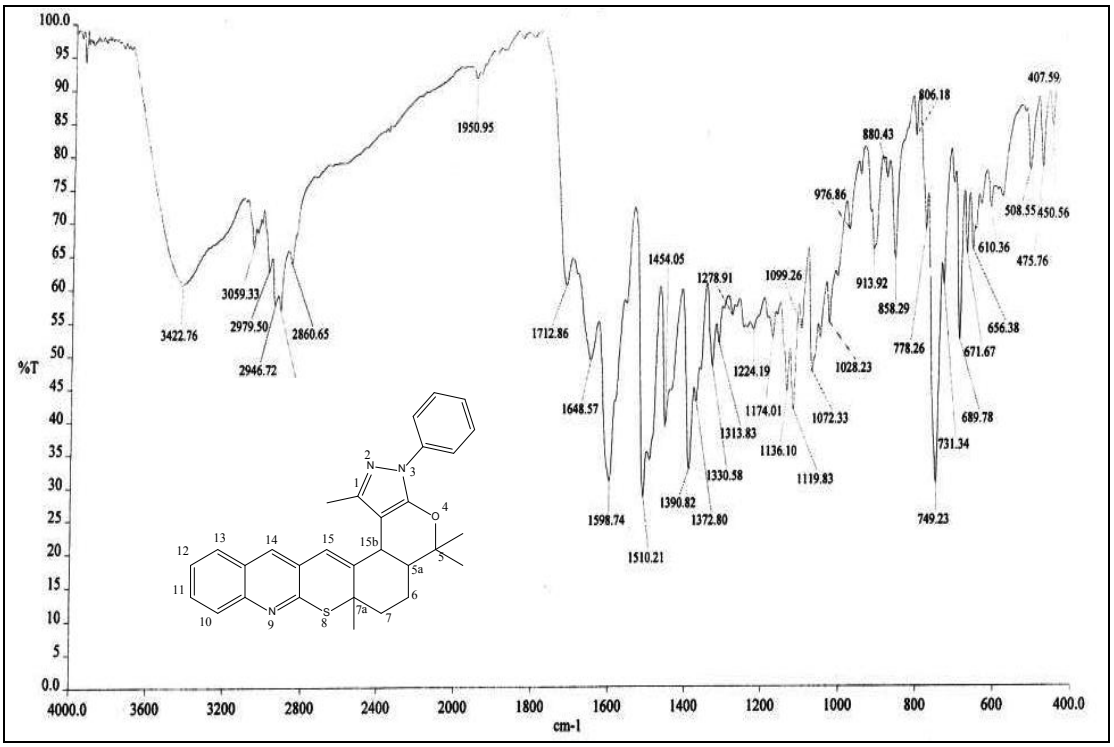
DEPT-135 spectrum of compound 5a



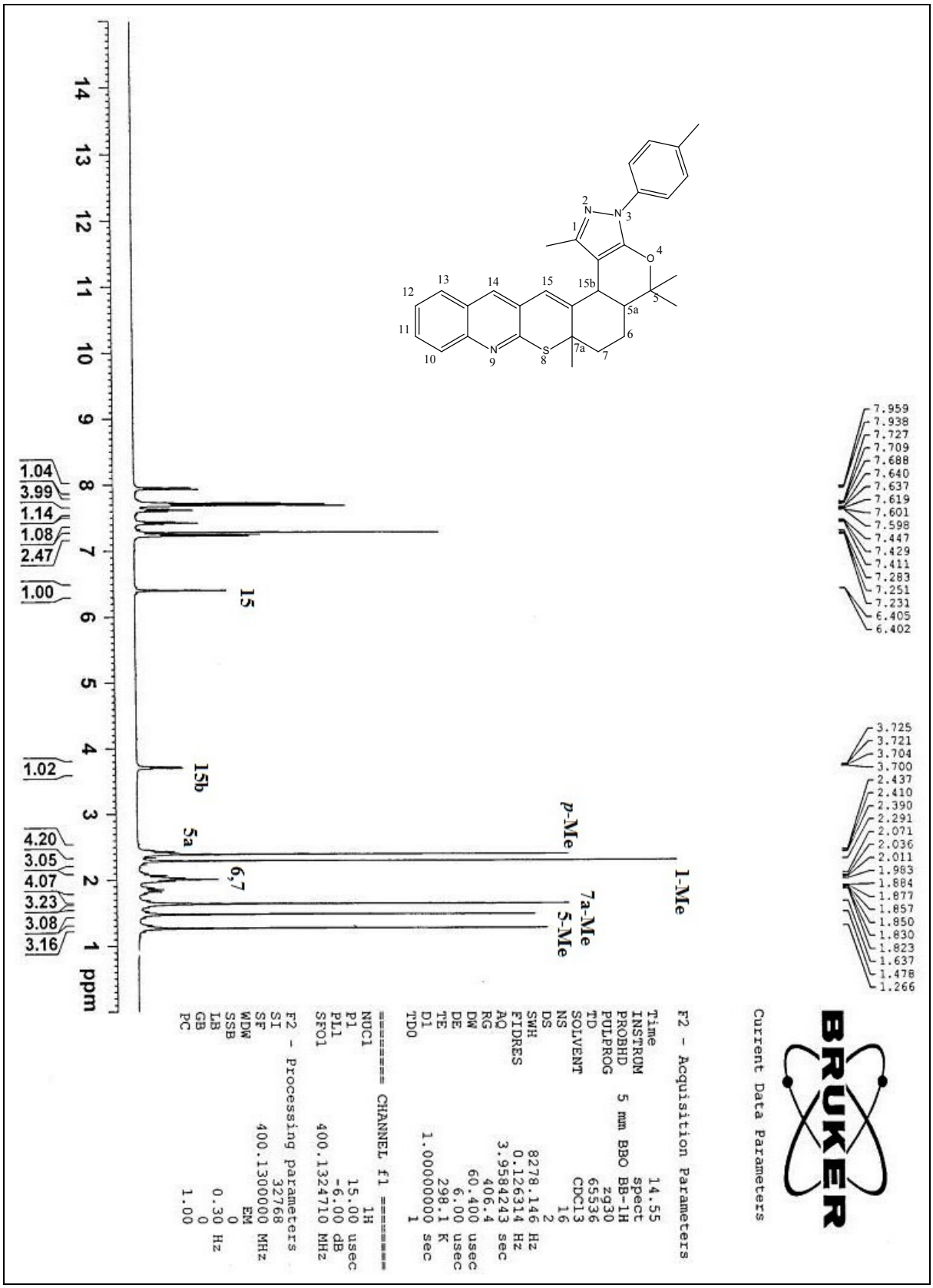
ESI-MS of compound 5a



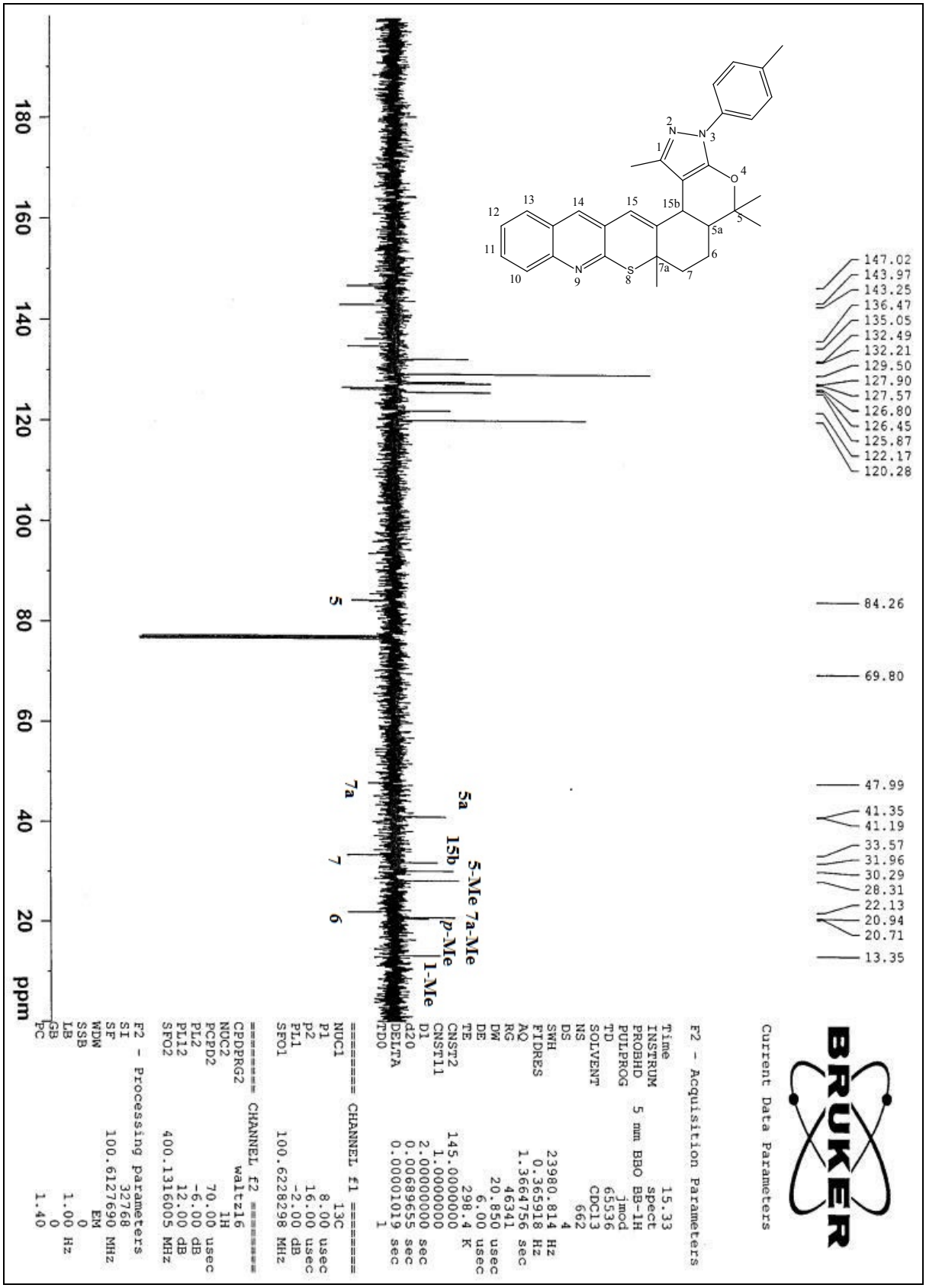
FT-IR spectrum of compound 5a



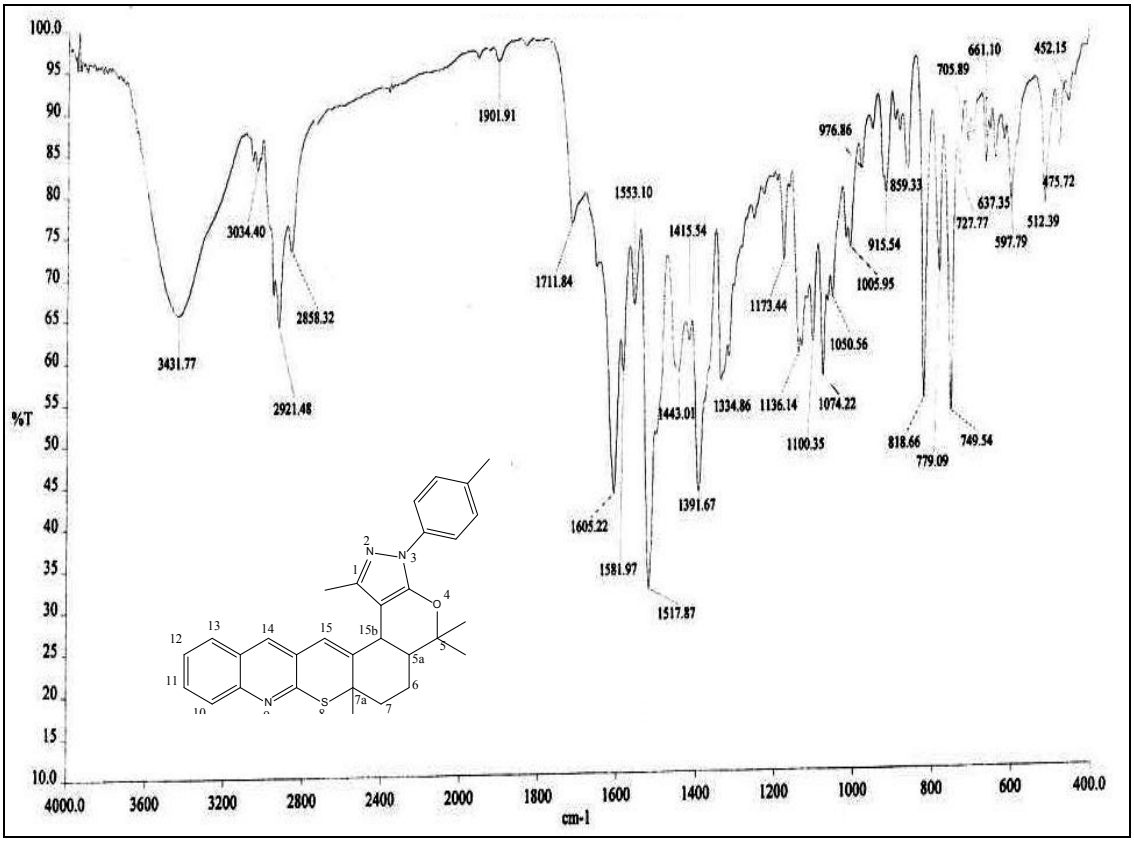
^{1}H NMR spectrum of compound 5b



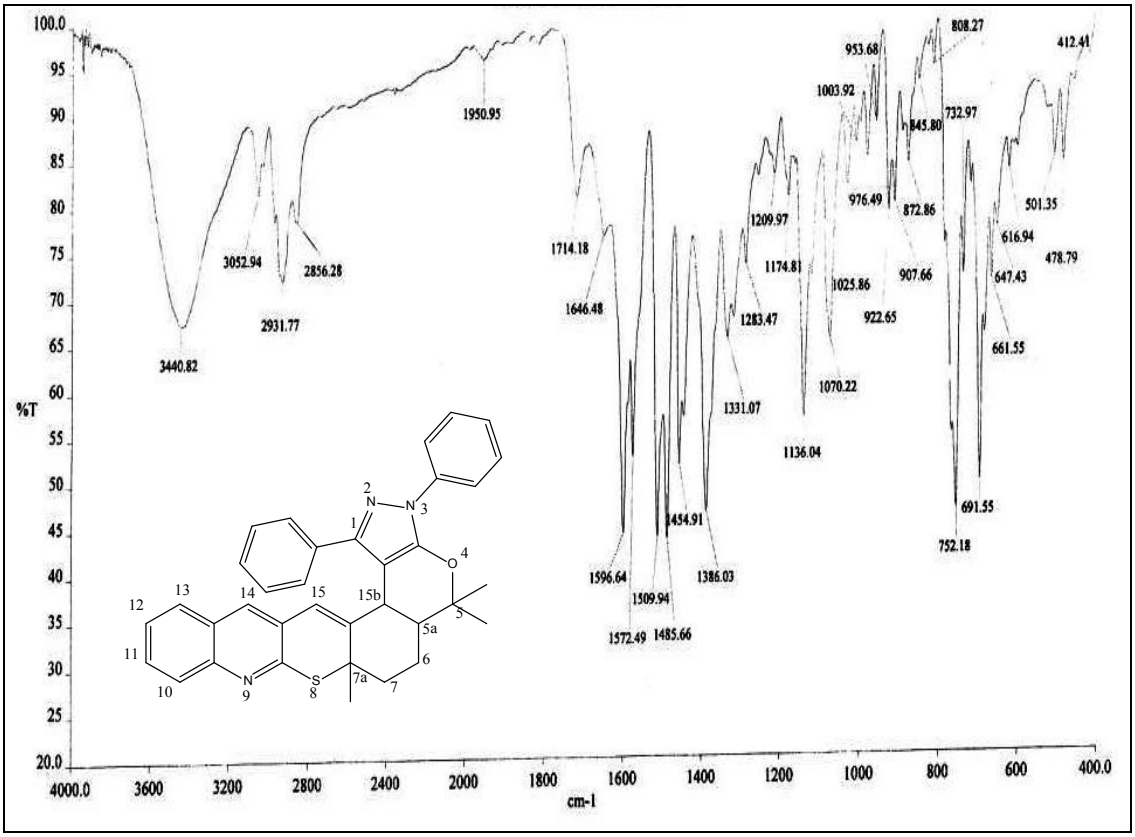
APT spectrum of compound 5b



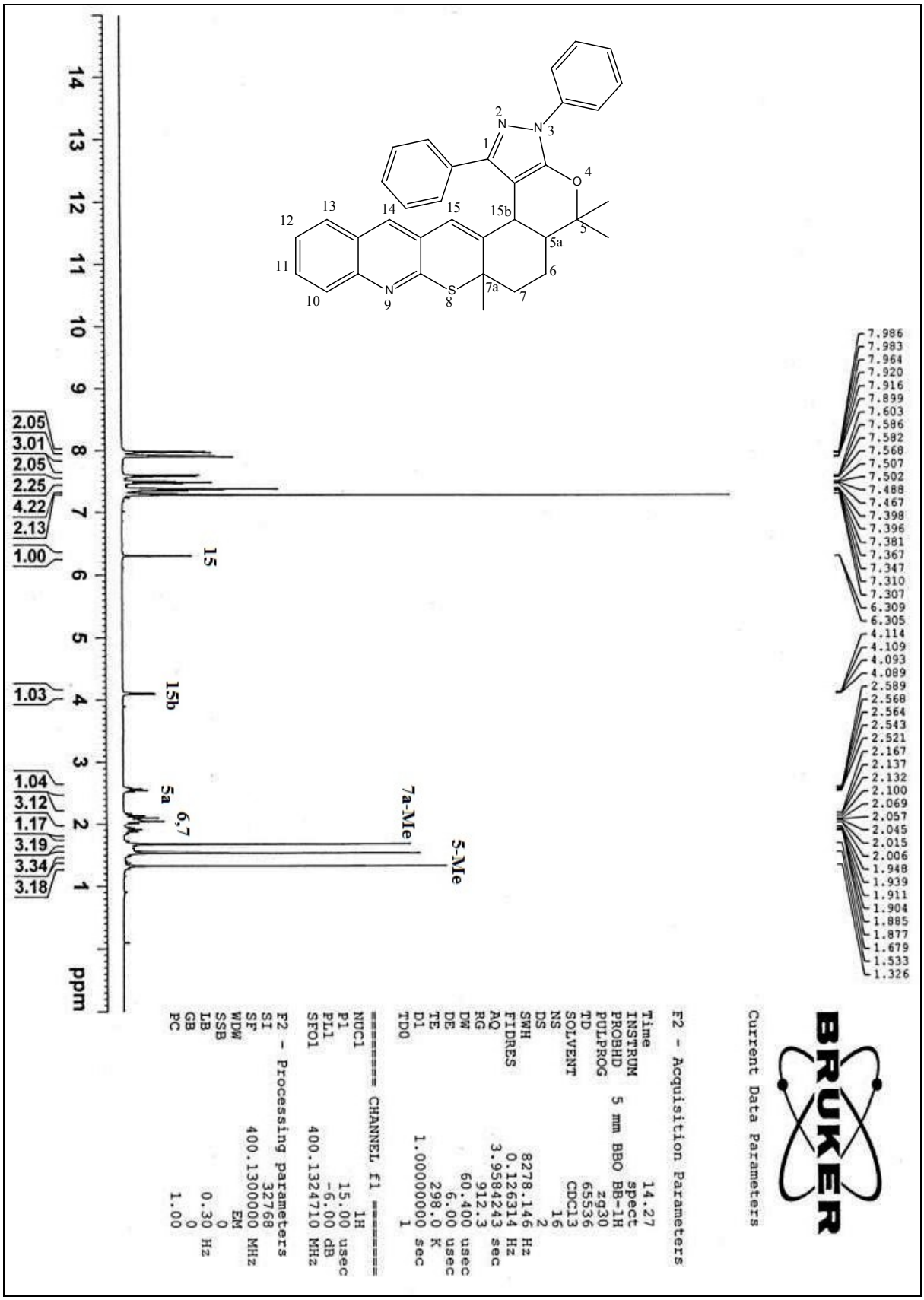
FT-IR spectrum of compound 5b



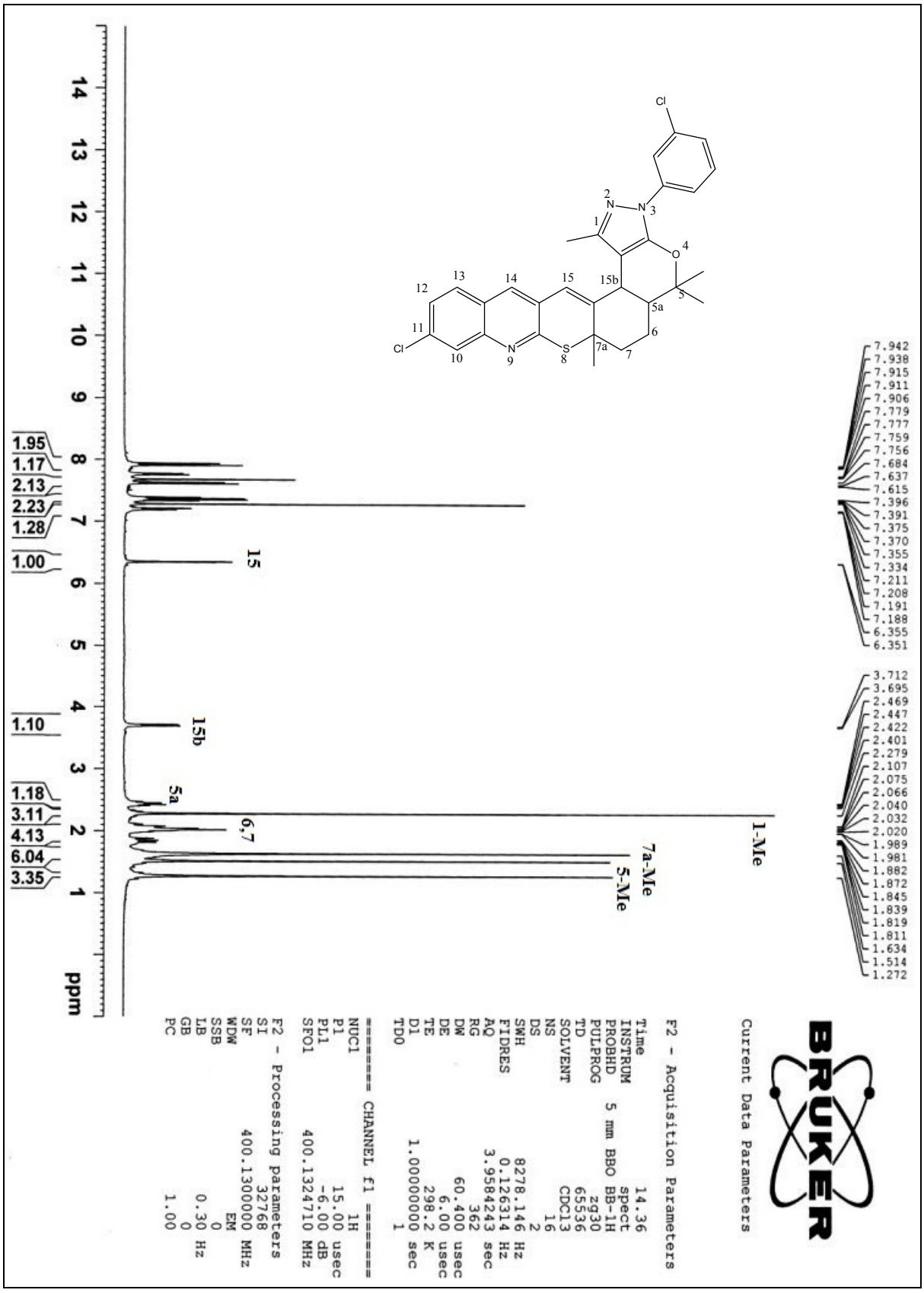
FT-IR spectrum of compound 5d



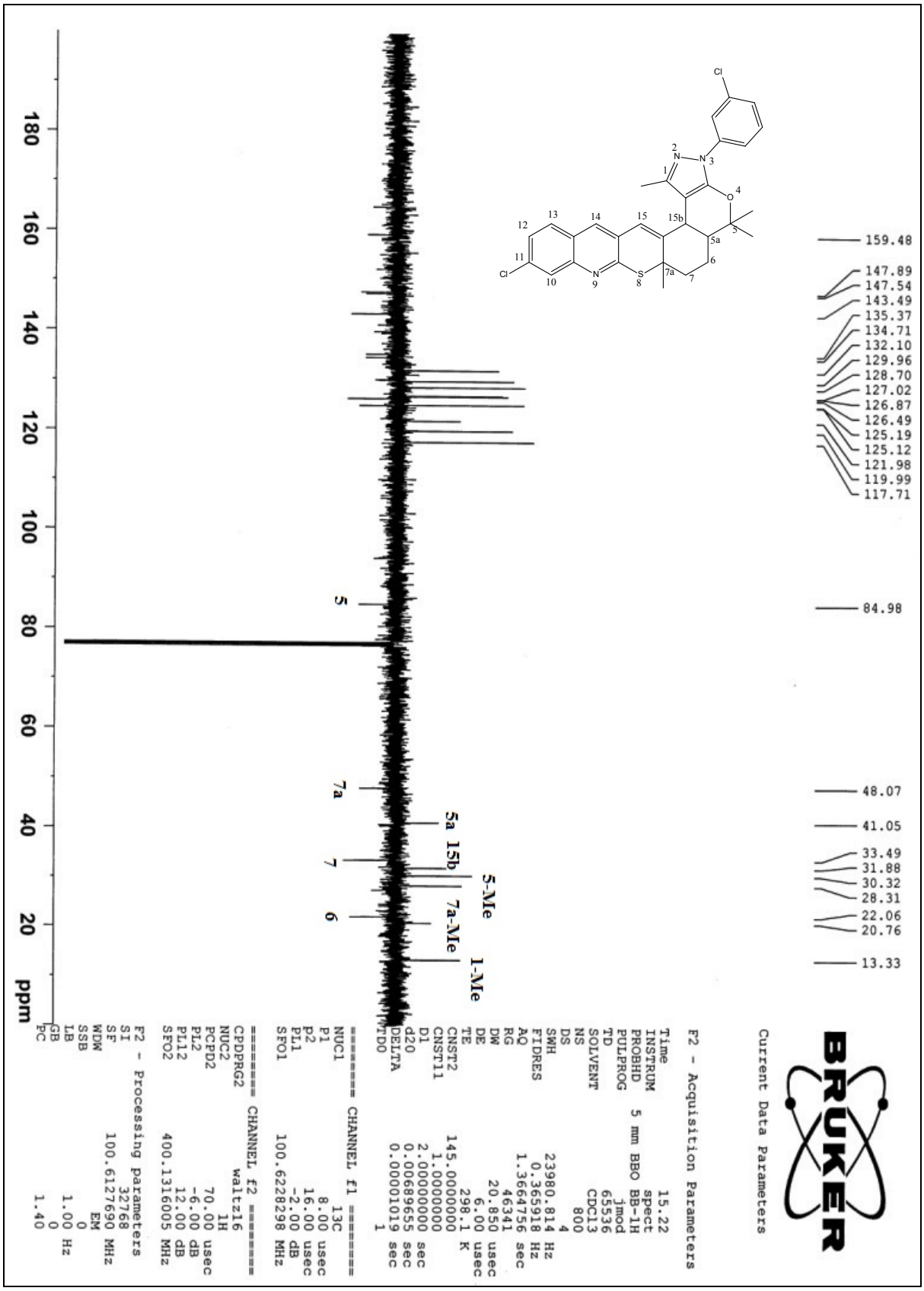
^{1}H NMR spectrum of compound 5d



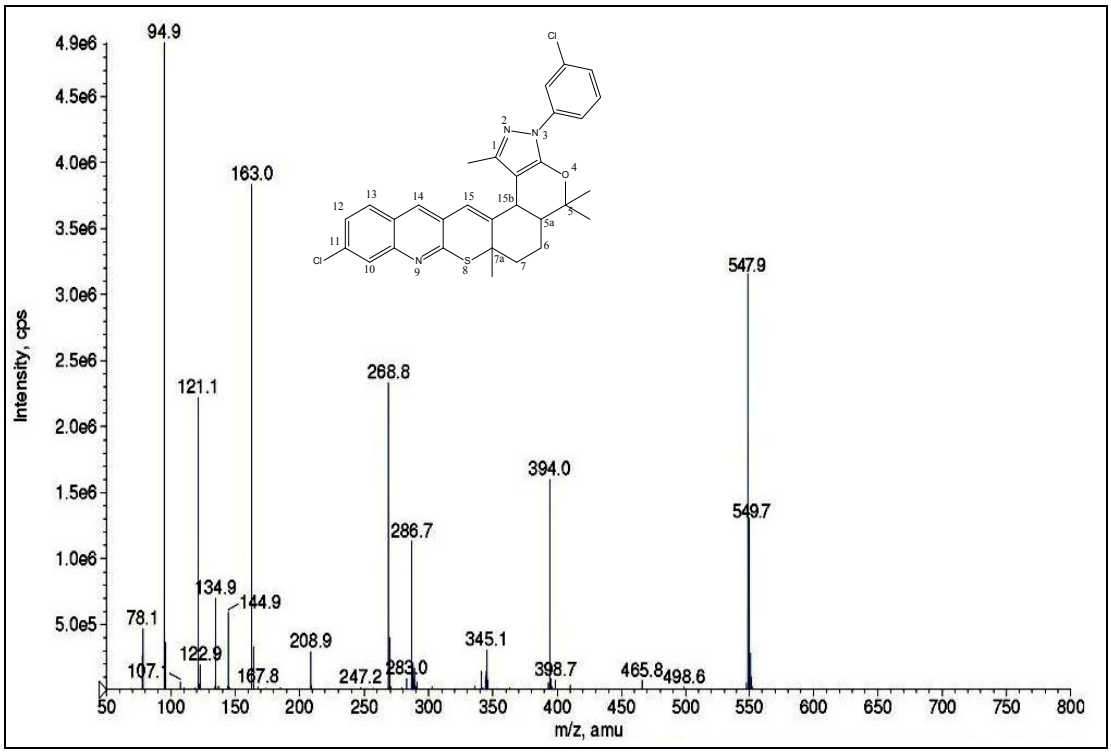
^{1}H NMR spectrum of compound 5i



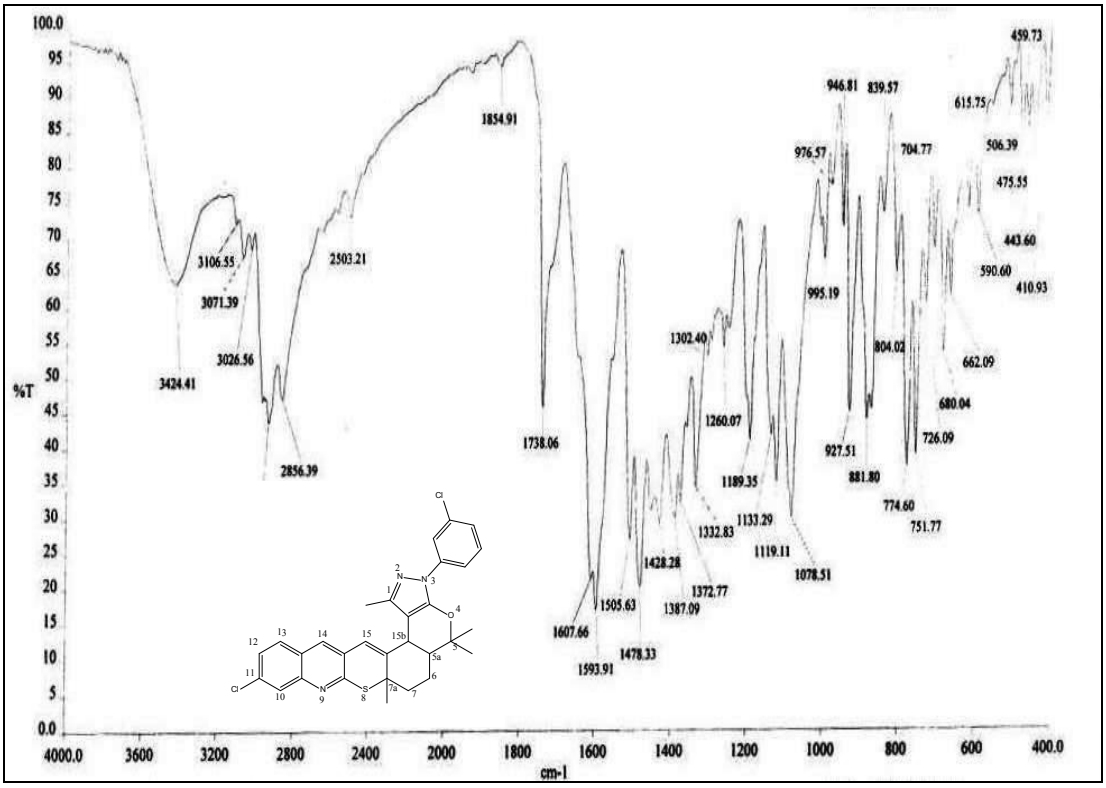
APT spectrum of compound 5i



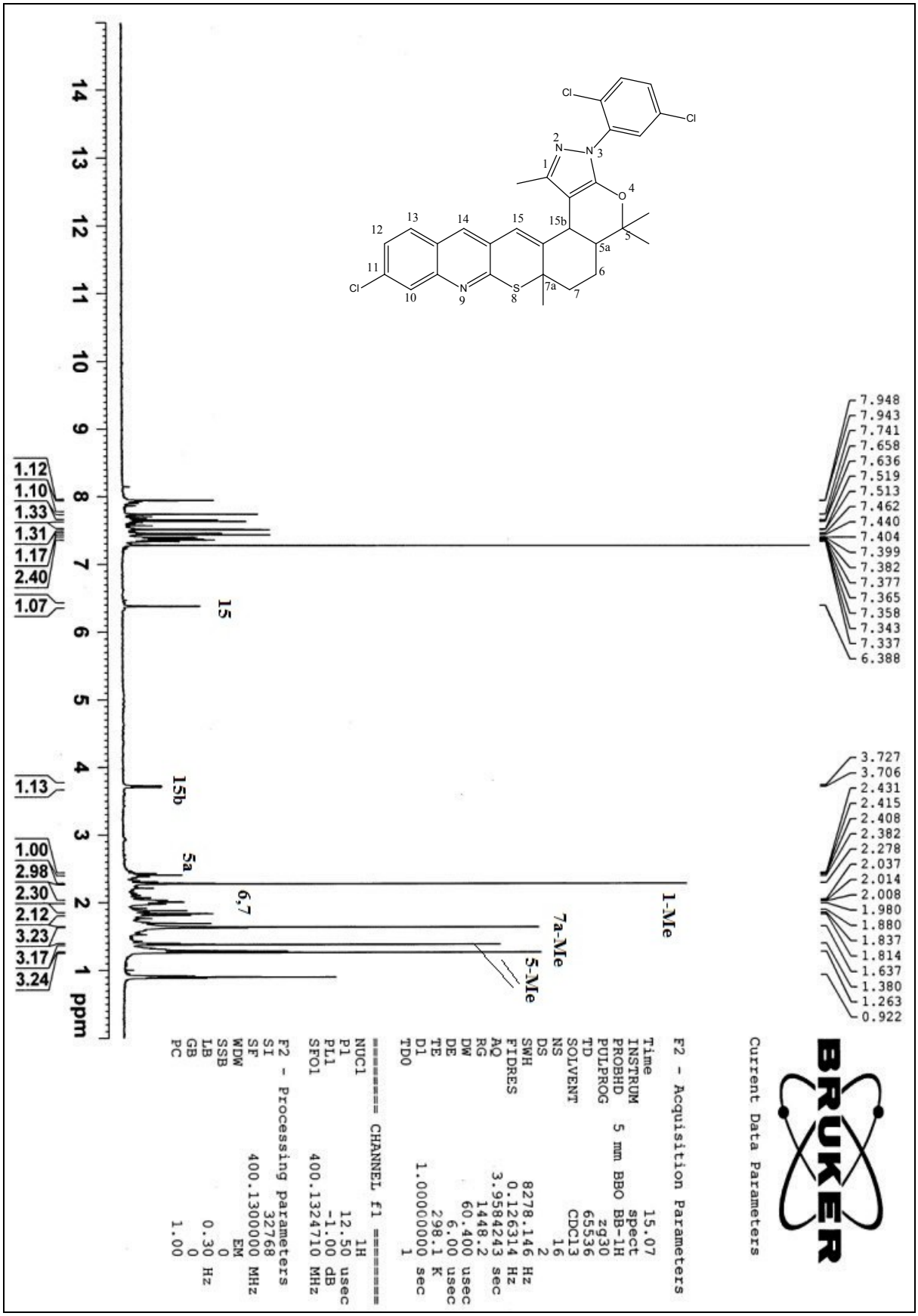
ESI-MS of compound 5i



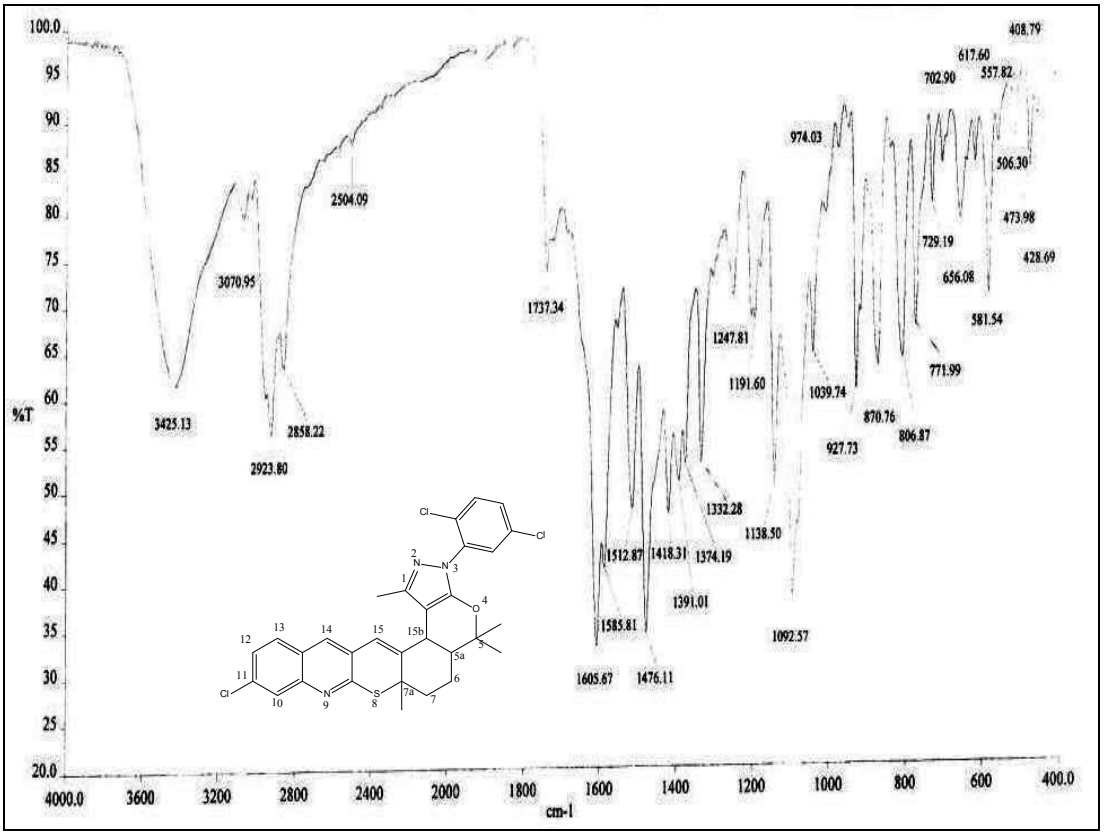
FT-IR spectrum of compound 5i



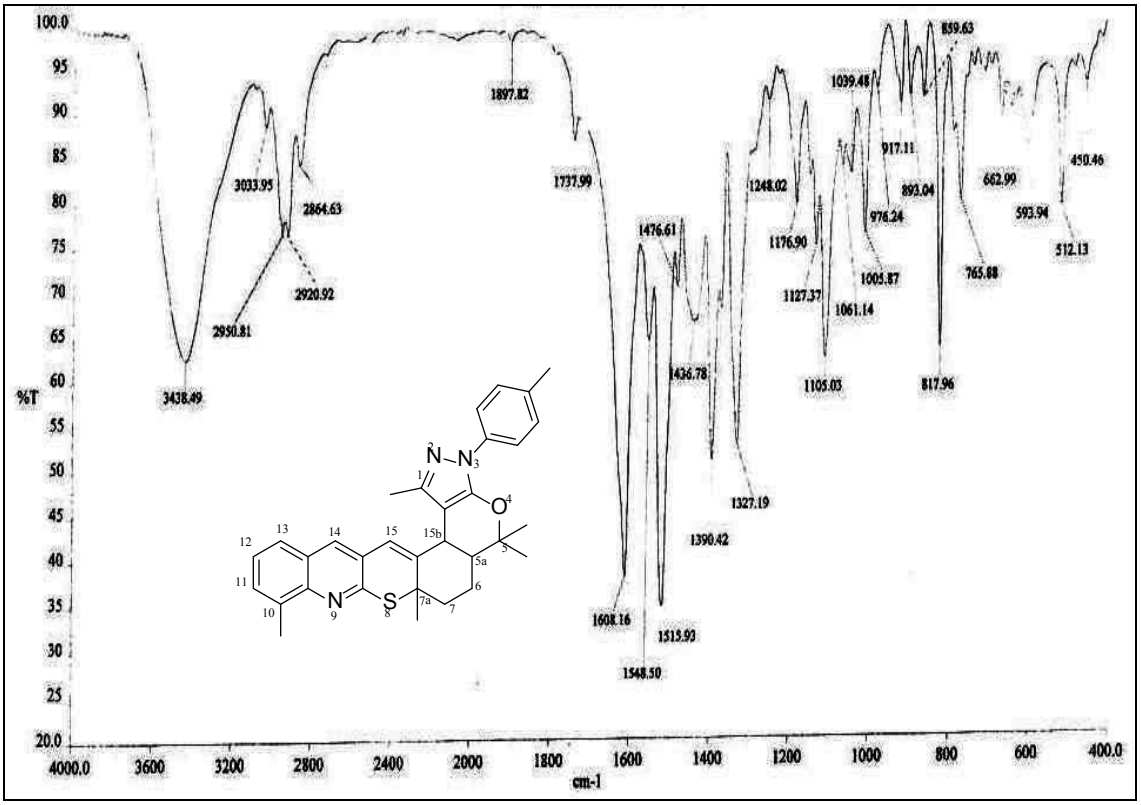
^{1}H NMR spectrum of compound 5k



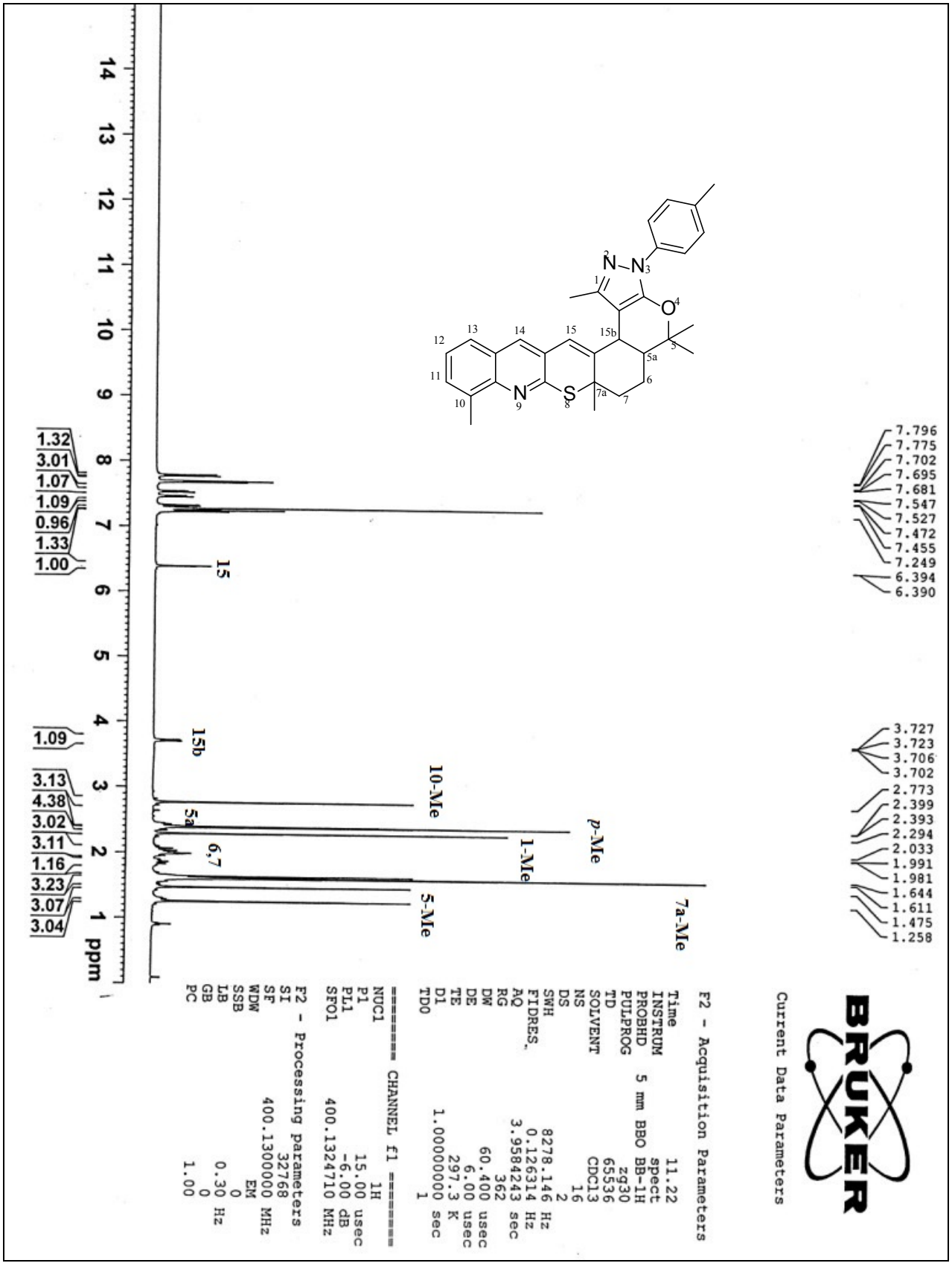
FT-IR spectrum of compound 5k



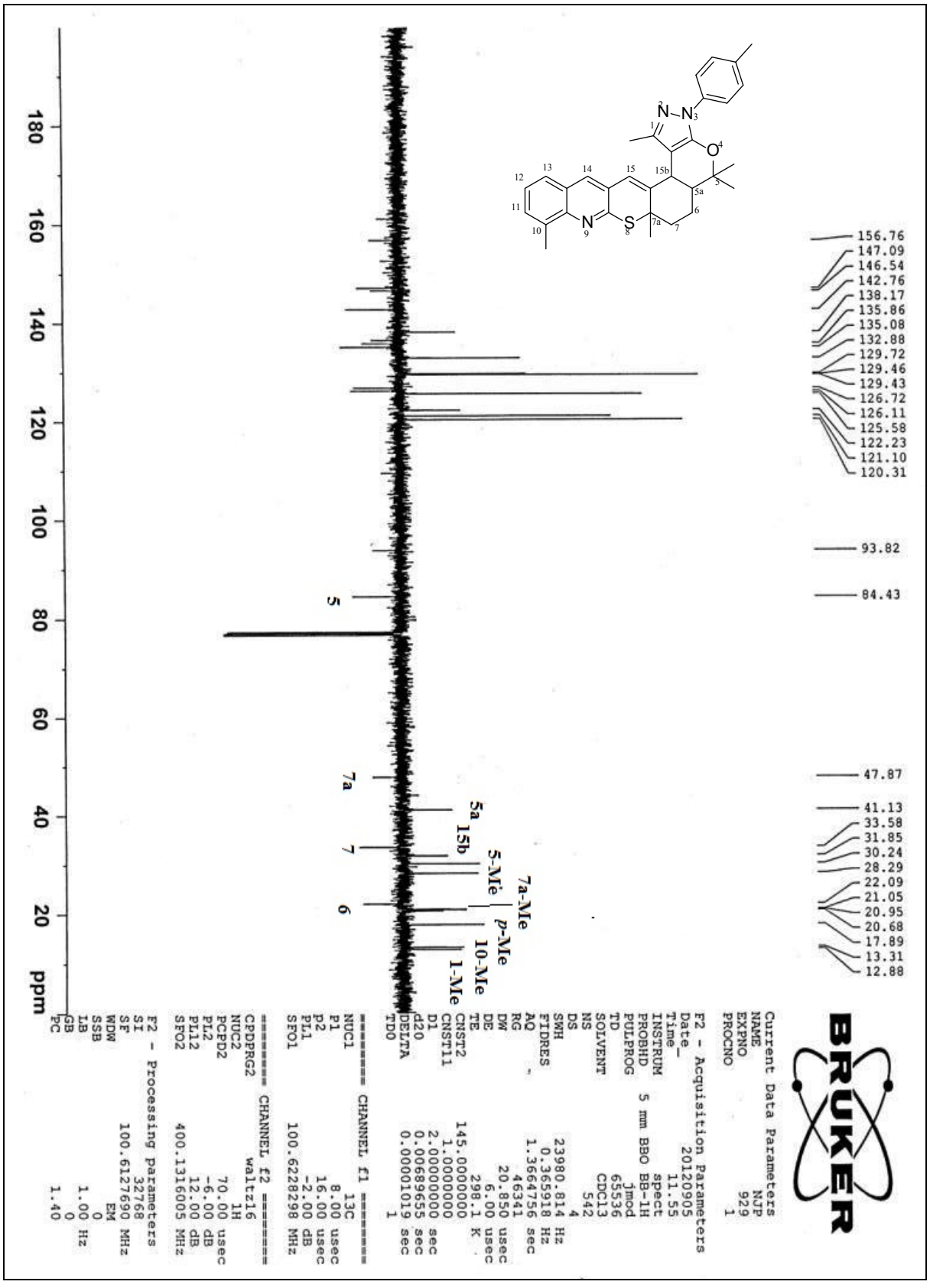
FT-IR spectrum of compound 5n



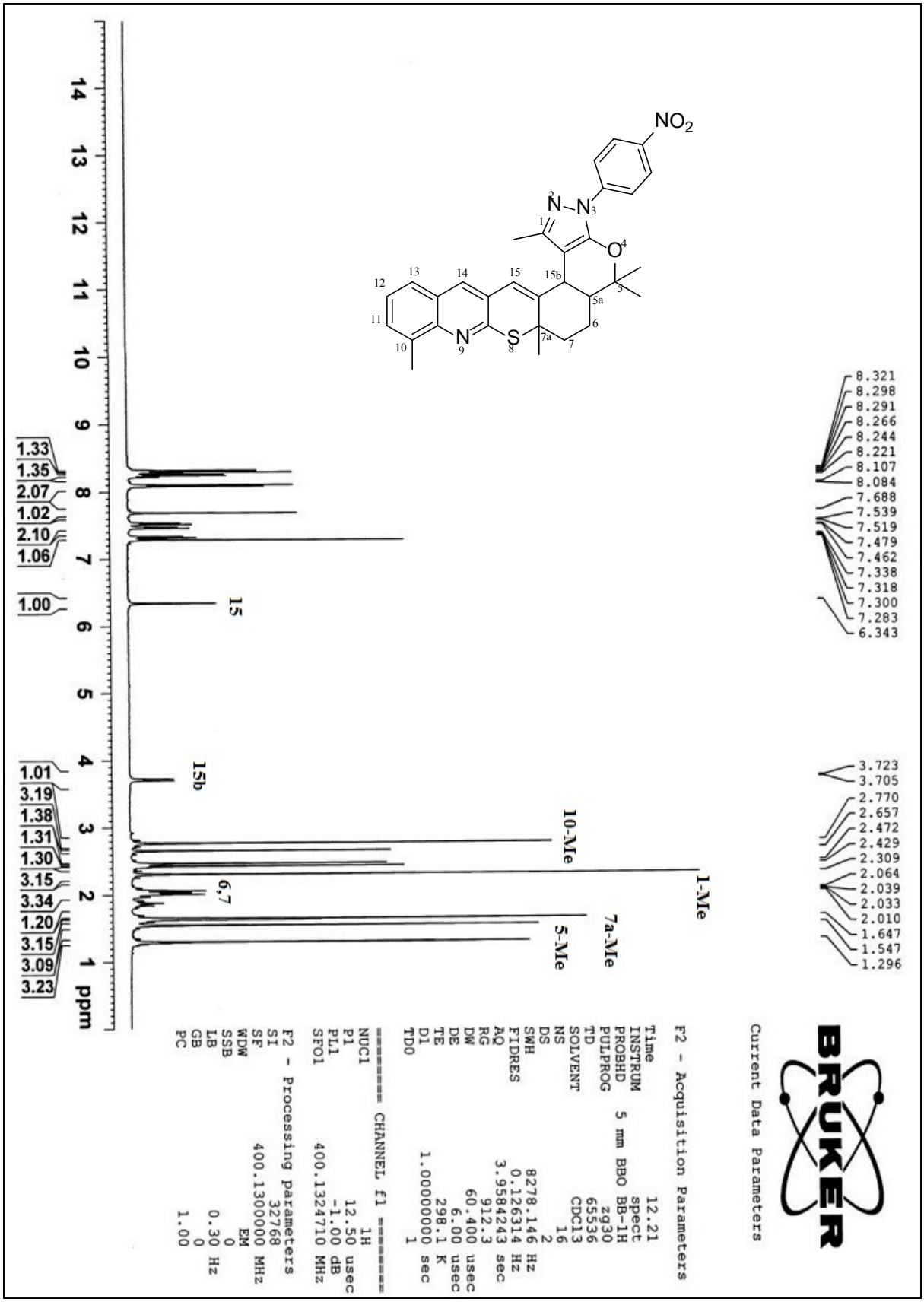
^{1}H NMR spectrum of compound 5n



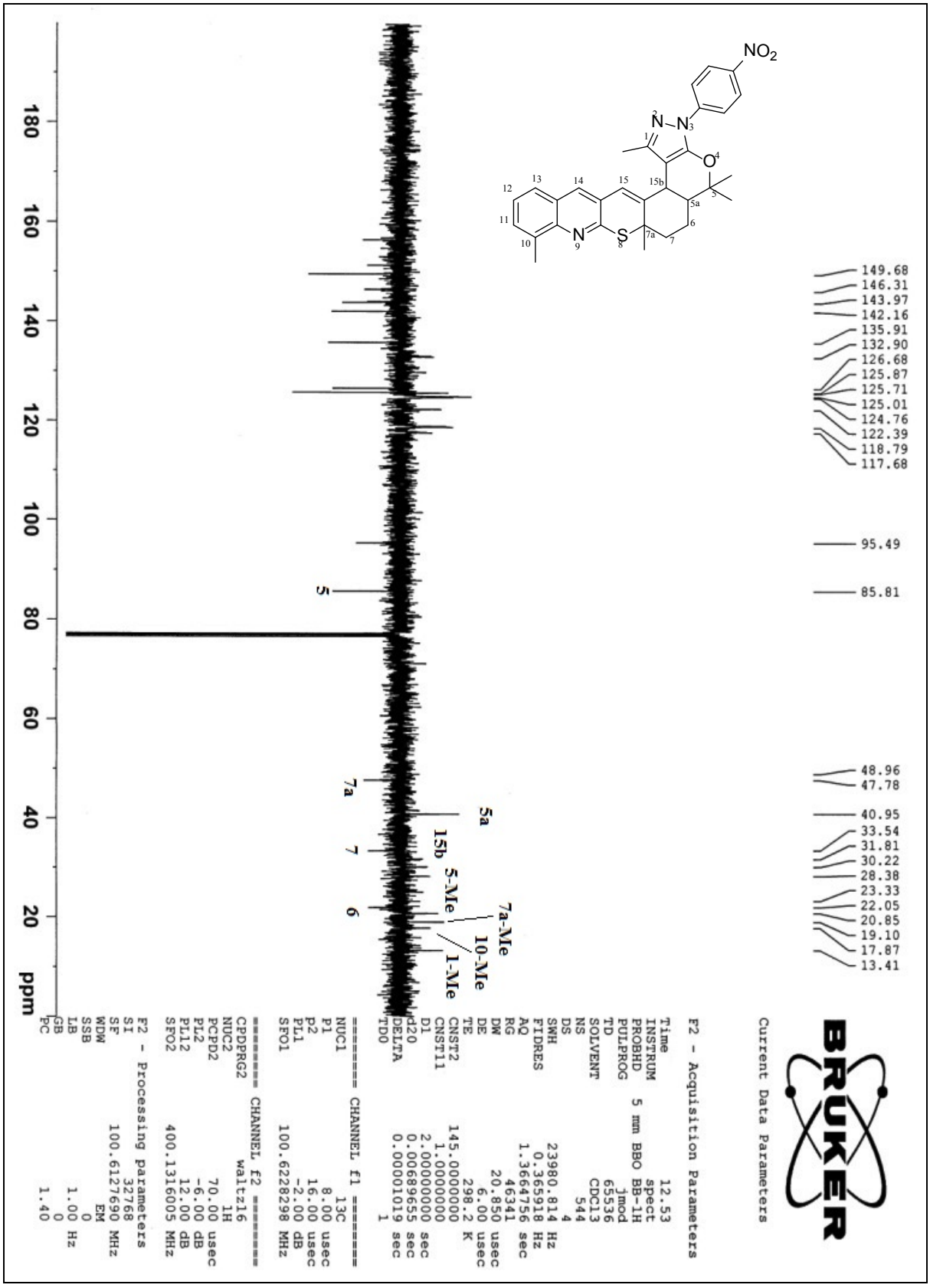
APT spectrum of compound 5n



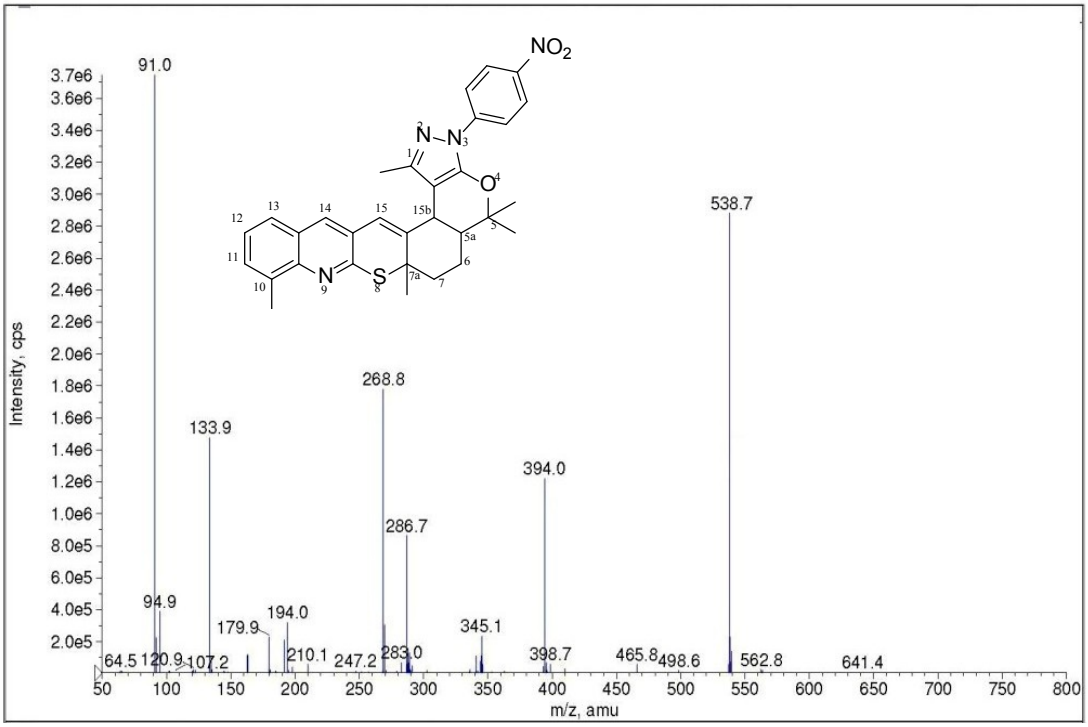
^{1}H NMR spectrum of compound 5r



APT spectrum of compound 5r



ESI-MS of compound 5r



FT-IR spectrum of compound 5r