

## An efficient synthesis of new polyfunctional hexahydro pyrido[1,2-*a*]pyrazin-1-ones

Yana Yu. Shmoylova, Yuri A. Kovygin, Irina V. Ledenyova, Mikhail A. Present, Elena D. Daeva, Sergey V. Baranin and Khidmet S. Shikhaliev

### Materials and Methods

#### Instrumentation

NMR  $^1\text{H}$  and  $^{13}\text{C}$  spectra were registered on Bruker AV600 (600 and 150.9 MHz, respectively) spectrometer in DMSO- $d_6$ , internal standard was TMS. Melting points were determined on Stuart SMP 30. Control of reagent and products individuality, qualitative analysis of reaction mass was performed by TLC on Merck TLC Silica gel 60 F254 chromatographic plate; eluents: methanol, chloroform and their mixtures in various ratios. The chromatograms were visualized by UV or iodine vapor.

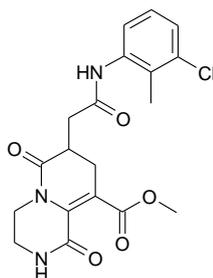
Product purity was monitored by high performance liquid chromatography with high resolution mass spectrometric electrospray ionization detection (HPLC-HRMS-ESI) in combination with UV detection. The analyzes were performed on Agilent 1260 Infinity chromatograph (Agilent Technologies, CA, USA) and Agilent 6230 TOF LC/MS high-resolution time-of-flight mass detector. The ionization block was double electrospray; the signals were recorded in positive polarity; nebulizer  $\text{N}_2$  20 psig; desiccant gas  $\text{N}_2$ , 6 ml  $\text{min}^{-1}$ , 325 °C; mass detection range is 50-2000 daltons. Capillary voltage 4.0 kV, fragmentator +191 V, skimmer +66 V, OctRF 750 V. Poroshell 120 EC-C18 column (4.6 x 50 mm; 2.7  $\mu\text{m}$ ) was used. Gradient elution: acetonitrile/water (0.1% formic acid); flow rate 0.4 ml  $\text{min}^{-1}$ . Software for processing research results - MassHunter Workstation/Data Acquisition V.06.00. Microwave reactor Milestone MicroSYNTH Mod. ACT36 - Rev - 01 - 03/06, voltage 230V, frequency 50Hz, two magnetrons with a total power of 1600 W, microwave frequency 2450 MHz.

#### Chemicals

#### Synthesis of 7-(2-arylamino-2-oxoethyl)-1,6-dioxo-1,3,4,6,7,8-hexahydro-2*H*-pyrido [1,2-*a*]pyrazine-9-carboxylates **3a-g** (general procedure).

A solution of substituted itaconimide **1a-g** (5 mmol) and alkyl (3-oxopiperazin-2-ylidene) ethyl acetate **2a,g** (5 mmol) is boiled in acetic acid (5 ml) with microwave activation (300 W) for 1-2 h. The precipitate formed is filtered off and recrystallized from a 2:1 mixture of dioxane and DMF.

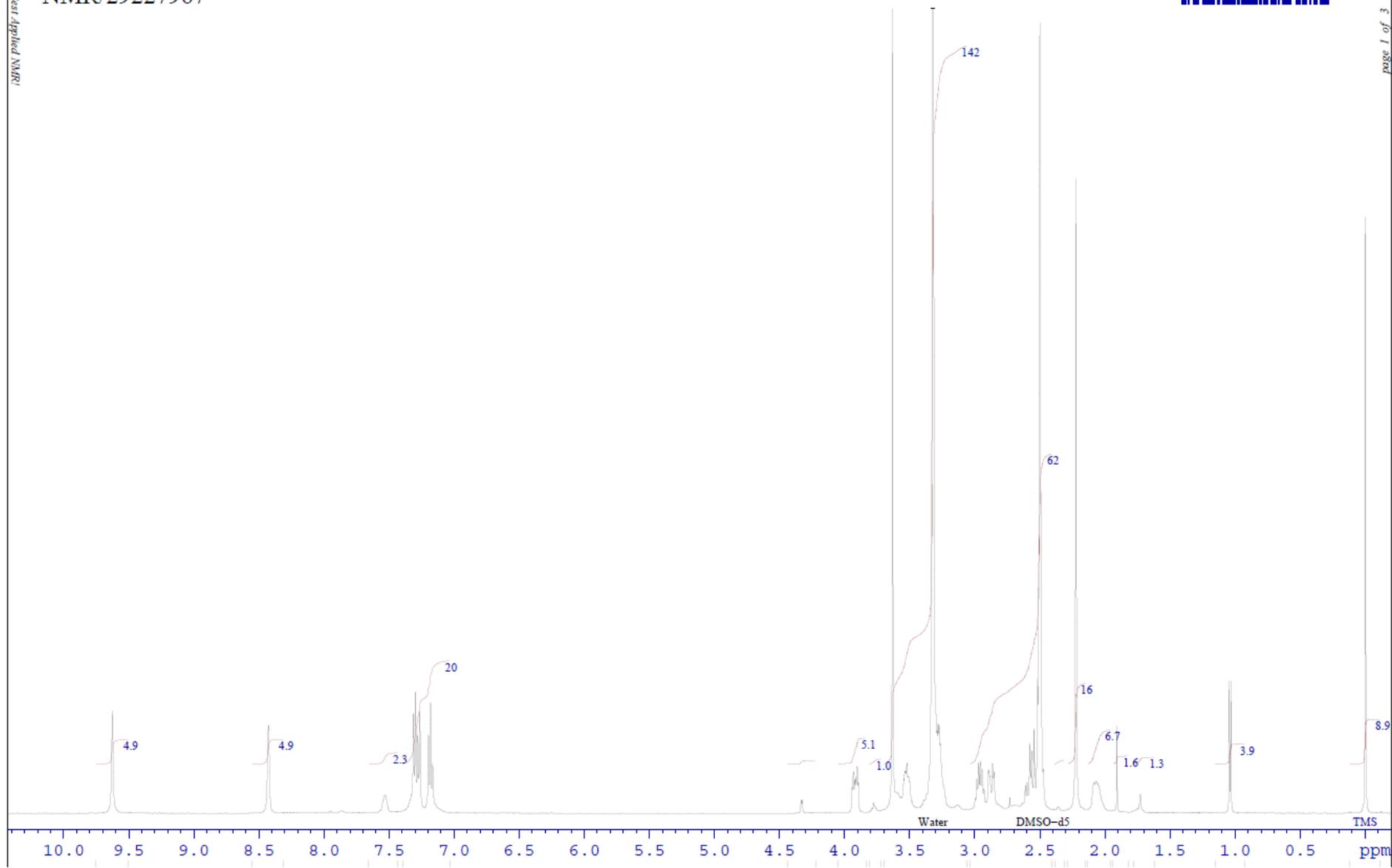
**Methyl 7-[2-(3-chloro-2-methylphenylamino)-2-oxoethyl]-1,6-dioxo-1,3,4,6,7,8-hexahydro-2H-pyrido[1,2-a]pyrazine-9-carboxylate (3a).**

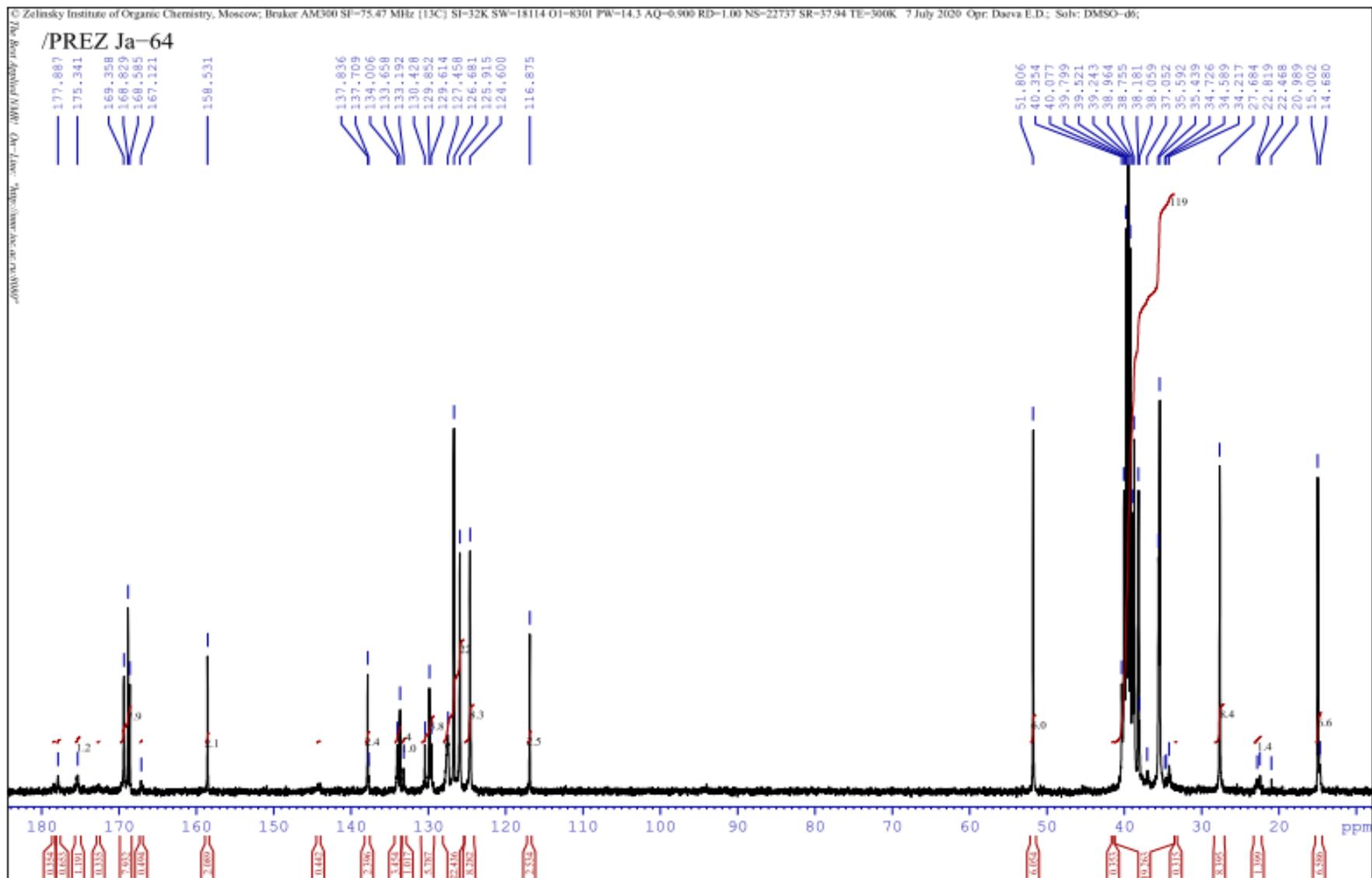


Yield: 1.53 g (76%), light yellow powdery compound, m.p. 235-236 °C.

<sup>1</sup>H NMR, (( $\delta$ , ppm.,  $J$ /Hz): 9.62 (1H, s, NH); 8.42(1H, s, NH); 7.16-7.31(3H, m, Ar); 3.94-3.90 (1H, m, CH<sub>2</sub><sup>8</sup>); 3.63(3H, s, O-CH<sub>3</sub>); 3.51-3.54 (1H, m, CH<sub>2</sub><sup>8</sup>); 3.28-3.26 (2H, m, CH<sub>2</sub><sup>3</sup>); 2.99-2.93 (1H, m, -CH<sup>7</sup>); 2.87 (1H, dd,  $J_1 = 12.7$ ,  $J_2 = 3.0$ , CH<sub>2</sub>-CO); 2.58-2.51 (2H, m, CH<sub>2</sub><sup>4</sup>); 2.49-2.47 (1H, m, CH<sub>2</sub>-CO); 2.22 (3H, s, CH<sub>3</sub>); <sup>13</sup>C NMR ( $\delta$ , ppm): 169.5 (COOMe); 168.83 (C<sup>6</sup>); 168.58 (C<sup>1</sup>); 158.53 (CONH); 137.83 (C<sup>1</sup>); 133.65 (C<sup>4</sup>); 129.85 (C<sup>9a</sup>); 126.68 (C<sup>3</sup>, C<sup>5</sup>); 124.60 (C<sup>2</sup>, C<sup>6</sup>); 116.87 (C<sup>9</sup>); 51.81 (OCH<sub>3</sub>); 38.75 (C<sup>8</sup>); 38.18 (C<sup>3</sup>); 35.59 (CH<sub>2</sub>-CO); 35.43 (C<sup>7</sup>); 27.68 (C<sup>4</sup>); 15.00 (CH<sub>3</sub>); HRMS (ESI): Found,  $m/z$  406.1166 [M+H]<sup>+</sup>. C<sub>19</sub>H<sub>20</sub>ClN<sub>3</sub>O<sub>5</sub>. Calculated, [M+H] 406.1165.

NMR/29227967

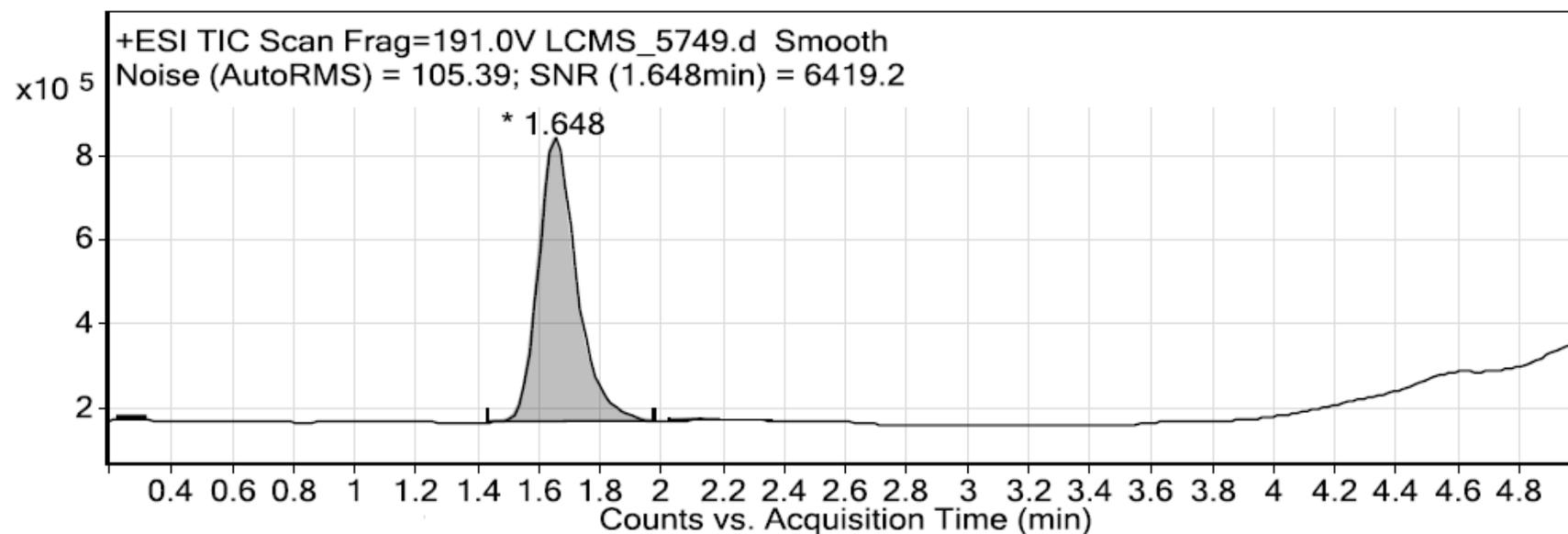




Data Filename	LCMS_5749.d	Sample Name	
Sample Type	Sample	Position	Vial 16
Instrument Name	Instrument 1	User Name	
Acq Method	ACN-H2O_60-40.m	Acquired Time	05-Nov-19 2:24:29 PM
IRM Calibration Status	Success	DA Method	13032017.m
Comment			
Sample Group		Info.	
Stream Name	LC 1	Acquisition SW	6200 series TOF/6500 series
		Version	Q-TOF B.06.01 (B6157)

### User Chromatograms

Fragmentor Voltage 191 Collision Energy 0 Ionization Mode ESI



#### Integration Peak List

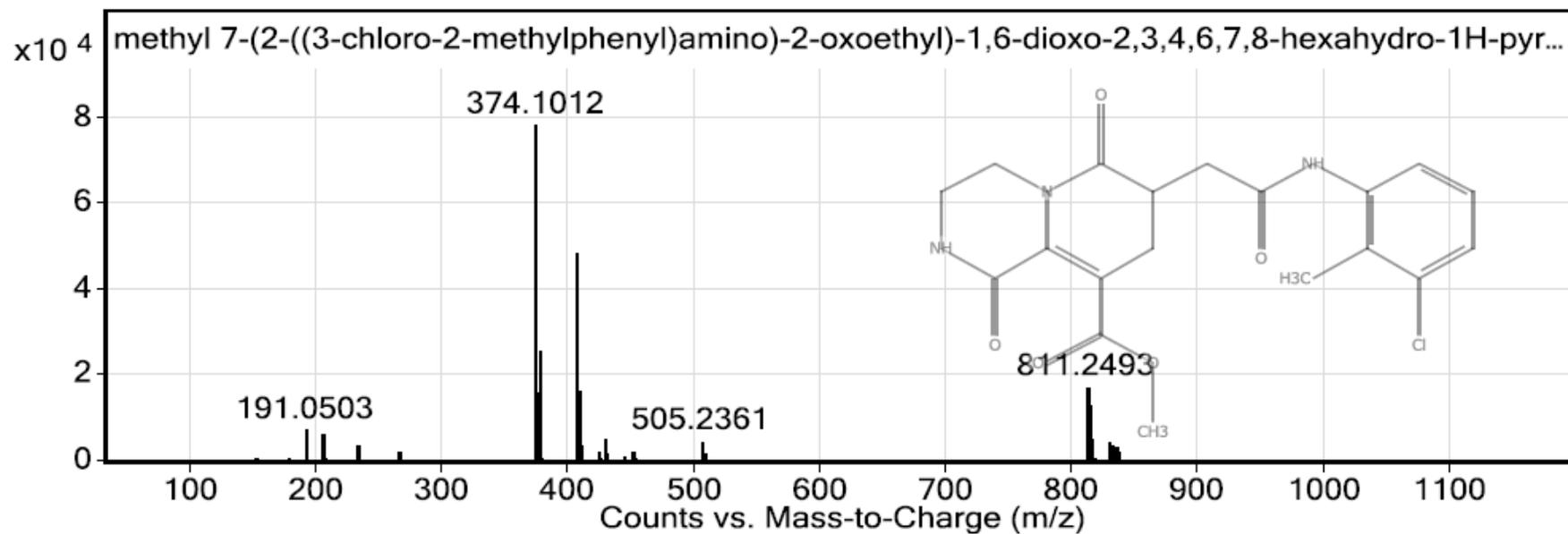
Peak	Start	RT	End	Height	Area	Area %	Signal To Noise
1	1.433	1.648	1.979	676498.98	5985640.88	100	6419.2

Spectrum Source  
Peak (1) in "+ TIC Scan Smo"

Fragmentor Voltage  
191

Collision Energy  
0

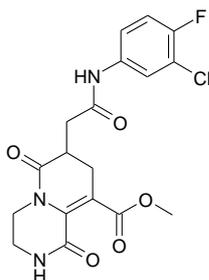
Ionization Mode  
ESI



Peak List

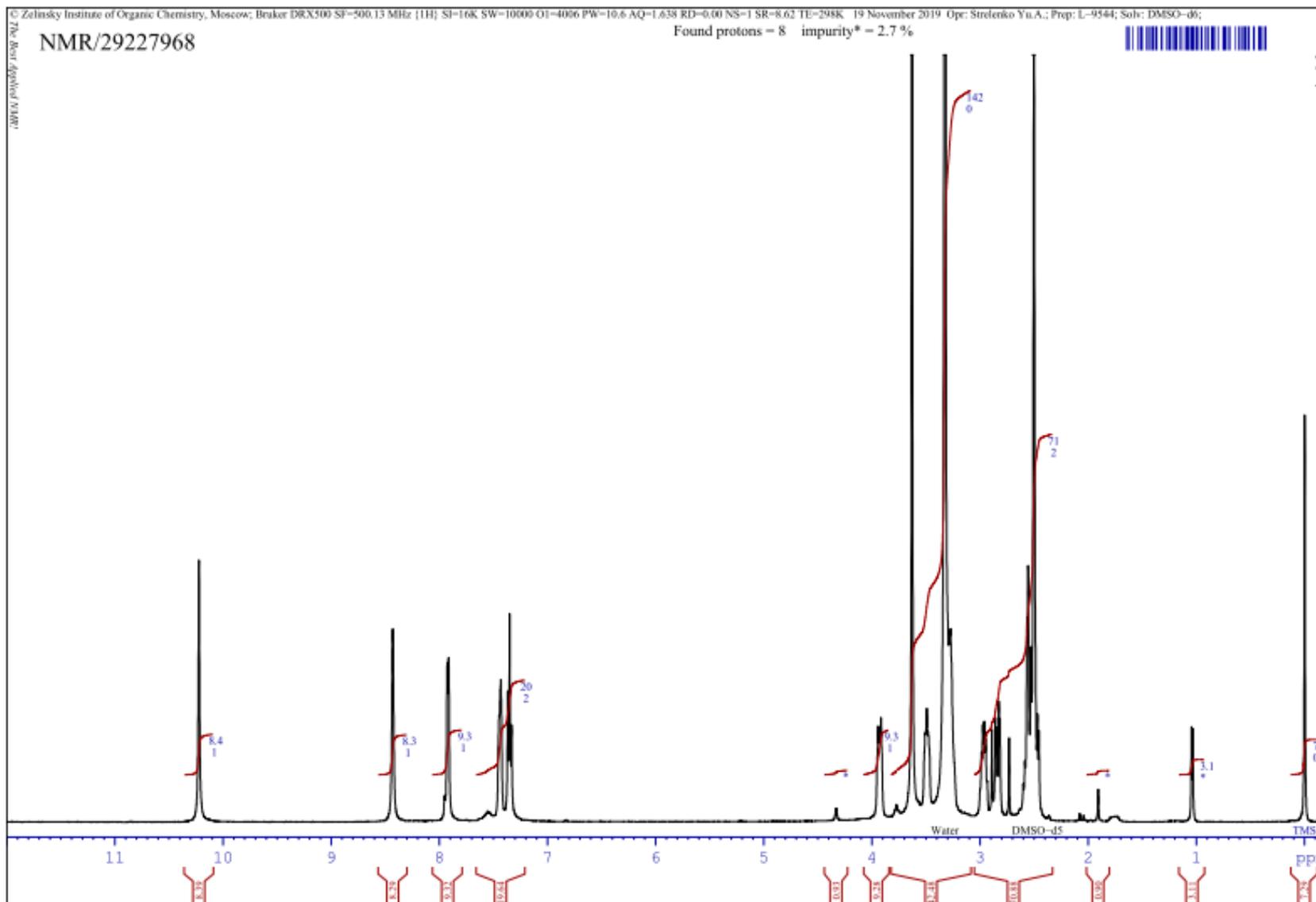
<i>m/z</i>	<i>z</i>	Abund
191.0503		7349.42
374.1012	1	78456.35
375.1044	1	15864.28
376.0993	1	25927.54
406.1166	1	48115.2
407.1314	1	10302.24
408.1261	1	16281.69
811.2493	1	17439.02
812.2521	1	7653.74

**Methyl 7-[2-(3-chloro-4-fluorophenylamino)-2-oxoethyl]-1,6-dioxo-1,3,4,6,7,8-hexahydro-2H-pyrido[1,2-a]pyrazine-9-carboxylate (3b).**

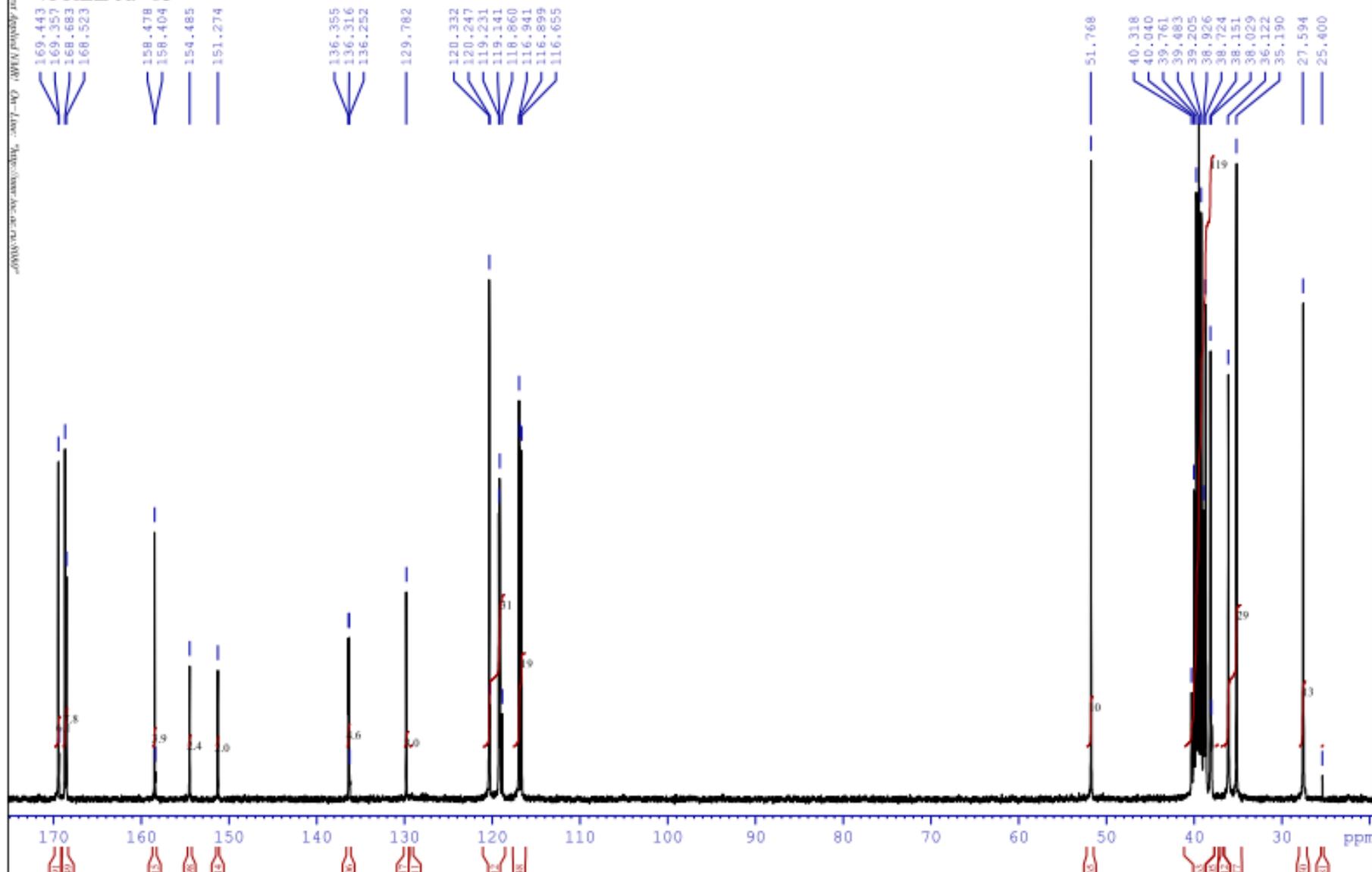


Yield: 1.49 g (73%), powdery compound, light beige, m.p. 219-220 °C.

$^1\text{H}$  NMR, ( $\delta$ , ppm.,  $J/\text{Hz}$ ): 10.22 (1H, s, NH); 8.43 (1H, s, NH); 7.33-7.93 (3H, m, Ar); 3.94-3.91 (1H, m,  $\text{CH}_2^8$ ); 3.63 (3H, s, O- $\text{CH}_3$ ); 3.49-3.37 (1H, m,  $\text{CH}_2^8$ ); 3.28-3.26 (2H, m,  $\text{CH}_2^3$ ); 2.98-2.94 (1H, m, - $\text{CH}^7$ ); 2.85 (1H, dd,  $J_1 = 15.8$ ,  $J_2 = 5.4$ ,  $\text{CH}_2\text{-CO}$ ); 2.54-2.51 (2H, m,  $\text{CH}_2^4$ ); 2.48-2.45 (1H, m,  $\text{CH}_2\text{-CO}$ );  $^{13}\text{C}$  NMR ( $\delta$ , ppm): 169.44 (COOMe); 168.68 ( $\text{C}^6$ ); 168.52 ( $\text{C}^1$ ); 158.48 (CONH); 154.48 ( $\text{C}^{1'}$ ); 151.27 ( $\text{C}^4$ ); 136.31 ( $\text{C}^{9a}$ ); 120.25 ( $\text{C}^{3'}$ ,  $\text{C}^{5'}$ ); 116.89 ( $\text{C}^{2'}$ ,  $\text{C}^{6'}$ ); 116.65 ( $\text{C}^9$ ); 51.76 (OCH<sub>3</sub>); 38.15 ( $\text{C}^8$ ); 38.03 ( $\text{C}^3$ ); 36.12 ( $\text{CH}_2\text{-CO}$ ); 35.19 ( $\text{C}^7$ ); 27.59 ( $\text{C}^4$ ); HRMS (ESI): Found,  $m/z$  410.0917 [ $\text{M}+\text{H}$ ] $^+$ .  $\text{C}_{18}\text{H}_{17}\text{ClFN}_3\text{O}_5$ . Calculated, [ $\text{M}+\text{H}$ ] 410.0915.



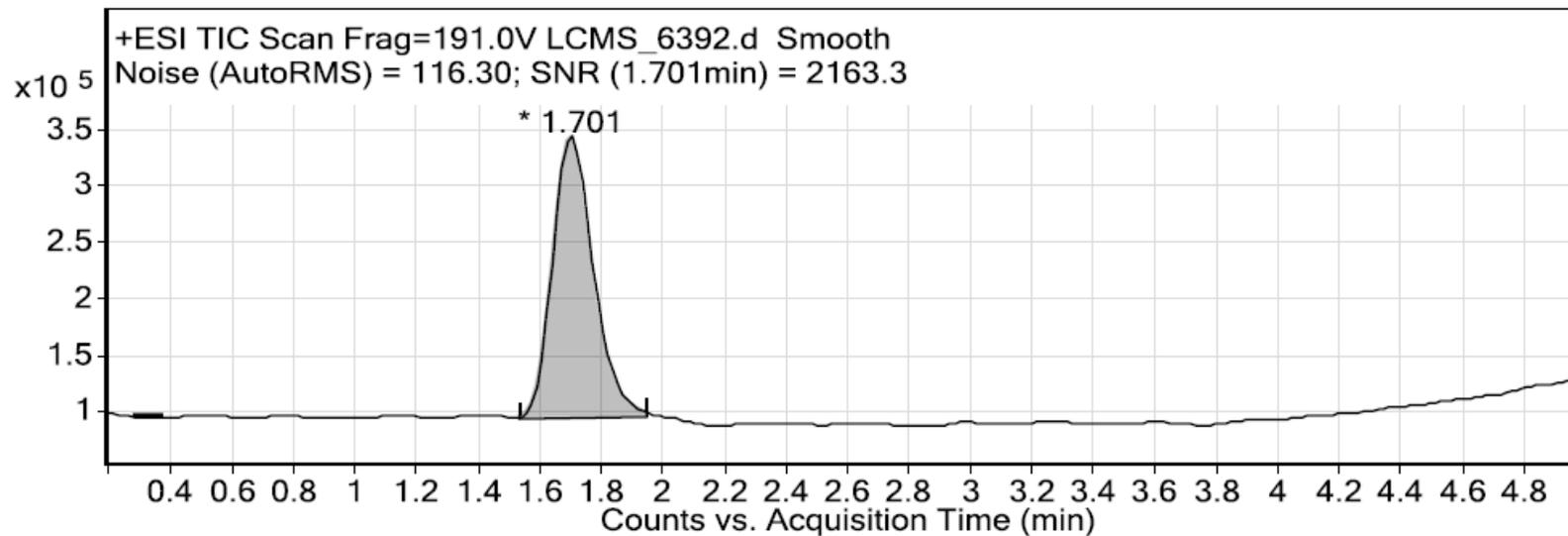
/PREZ Ja-65



**Data File** LCMS\_6392.d      **Sample Name**  
**Sample Type** Sample      **Position** Vial 21  
**Instrument Name** Instrument 1      **User Name**  
**Acq Method** ACN-H2O\_60-40.m      **Acquired Time** 28-Feb-20 2:20:07 PM  
**IRM Calibration Status** Success      **DA Method** 13032017.m  
**Comment**

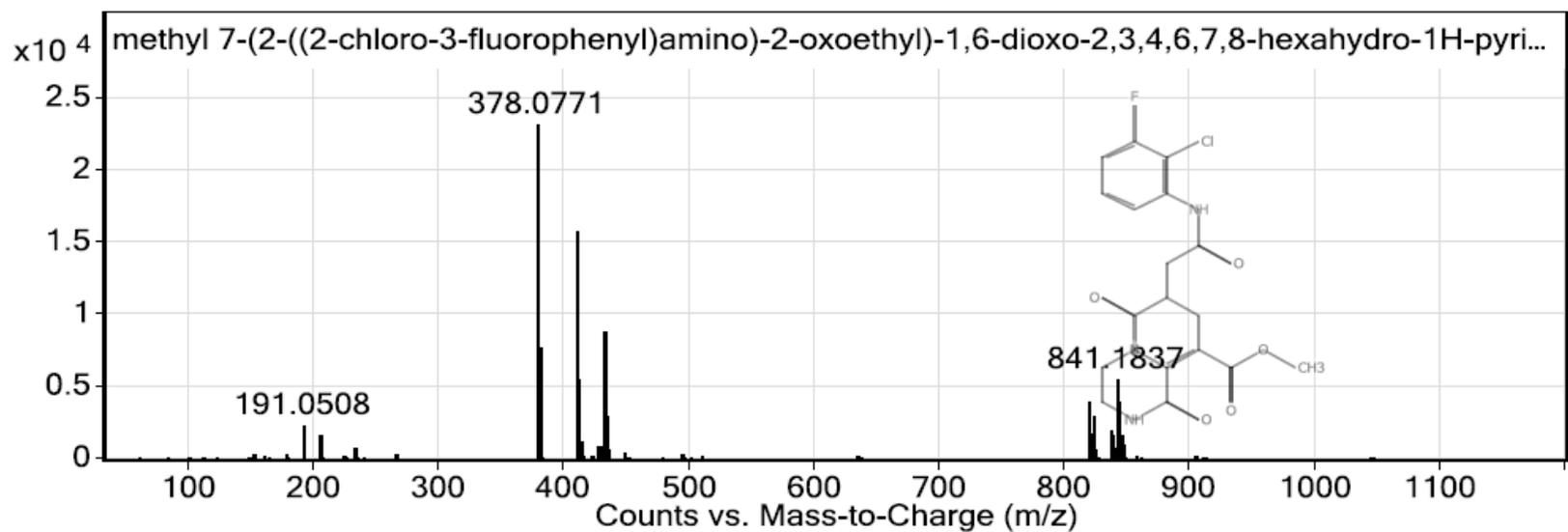
**Sample Group** Info.  
**Stream Name** LC 1      **Acquisition SW** 6200 series TOF/6500 series  
    **Version** Q-TOF B.06.01 (B6157)

**Fragmentor Voltage** 191    **Collision Energy** 0    **Ionization Mode** ESI



**User Chromatogram Peak List**

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1.701	251586.75	100	2389998.43	100	100	2163.3	1.34	0.414

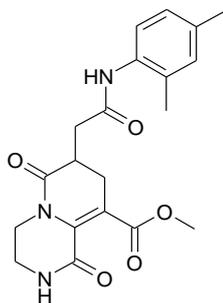


**MS Spectrum Peak List**

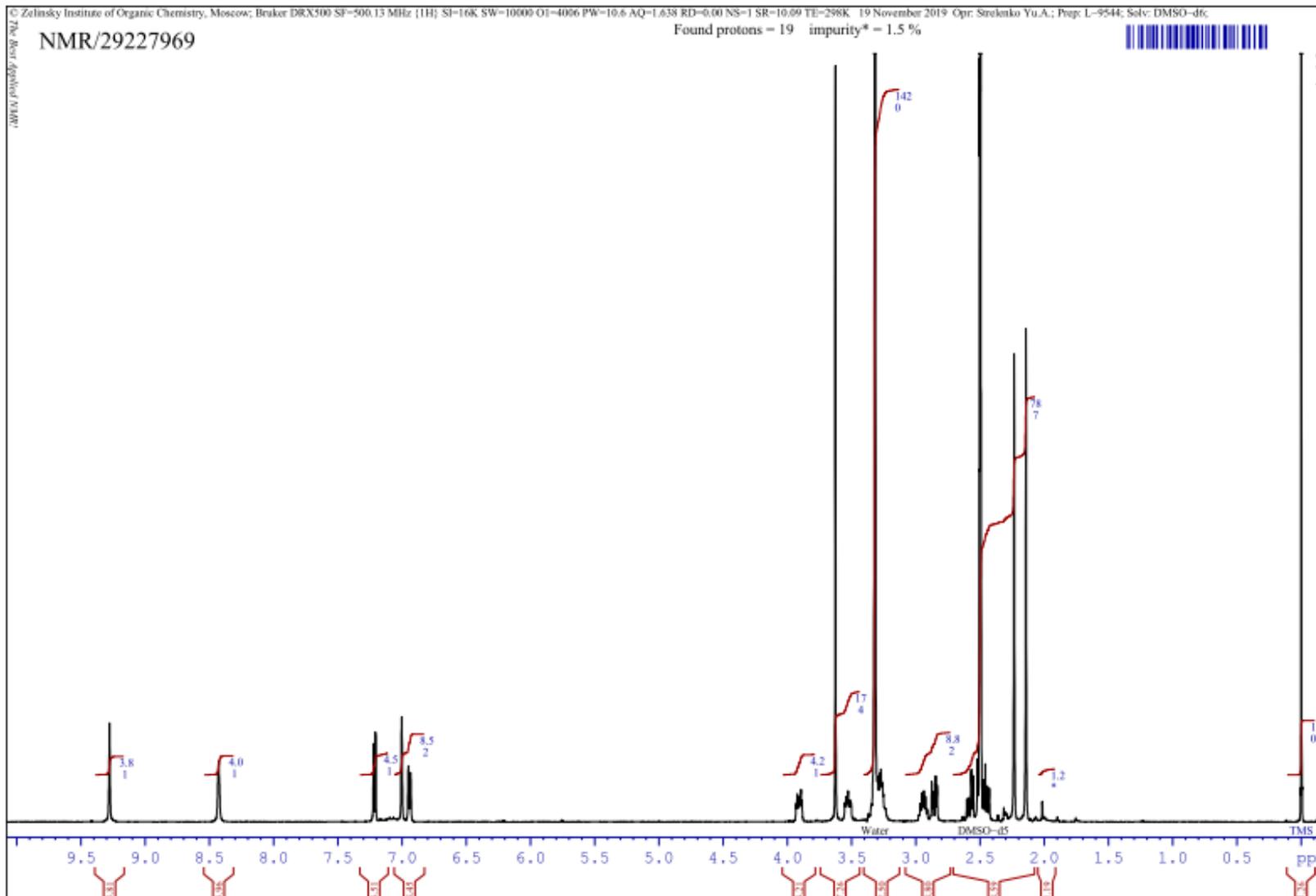
<i>m/z</i>	<i>z</i>	Abund
378.0771	1	23274.07
379.0796	1	4626.31
380.075	1	7767.79
410.0917	1	15807.02
411.1071	1	3427.74
412.1025	1	5530.24
432.0867	1	8975.86
819.2018	1	4017.56
841.1837	1	5541.96
843.1811	1	4090.08

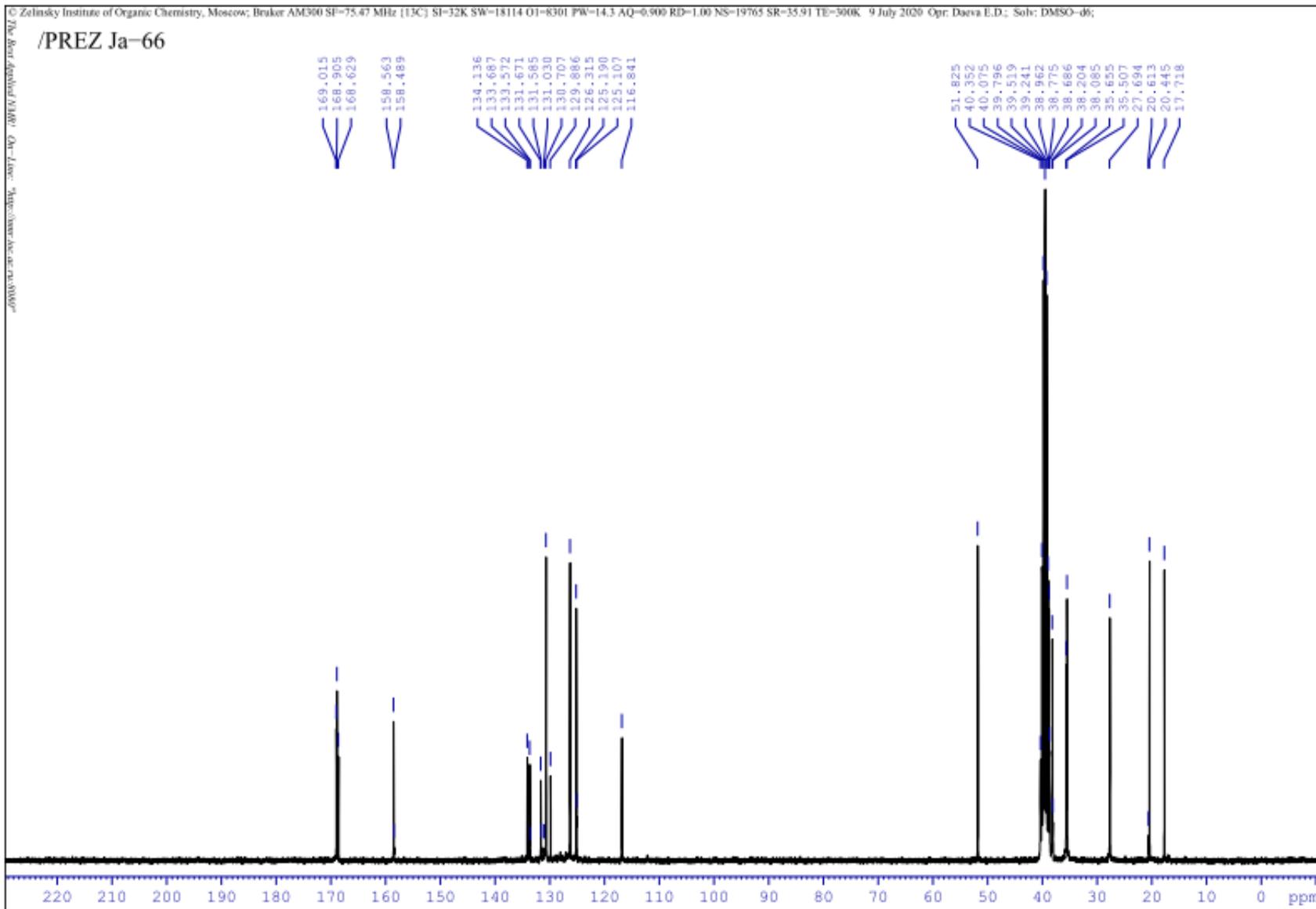
**Methyl 7-[2-(2,4-dimethylphenylamino)-2-oxoethyl]-1,6-dioxo-1,3,4,6,7,8-hexahydro-2H-pyrido[1,2-a]pyrazine-9-carboxylate (3c).**

Yield: 1.31g (68%), powdery compound of a light white color; m.p. 224-225 °C.



$^1\text{H}$  NMR, ( $\delta$ , ppm.,  $J/\text{Hz}$ ): 9.27 (1H, s, NH) 8.42(1H, s, NH); 6.93-7.22 (3H, m, Ar); 3.93-3.88 (1H, m,  $\text{CH}_2^8$ ); 3.62 (3H, s, O- $\text{CH}_3$ ) 3.55-3.51 (1H, m,  $\text{CH}_2^8$ ); 3.30-3.25 (2H, m,  $\text{CH}_2^3$ ); 2.96-2.91 (1H, m,  $-\text{CH}^7$ ); 2.85 (1H, dd,  $J_1 = 15.4$ ,  $J_2 = 5.5$ ,  $\text{CH}_2\text{-CO}$ ); 2.54-2.52 (2H, m,  $\text{CH}_2^4$ ); 2.45 (1H dd,  $J_1 = 15.3$ ,  $J_2 = 7.8$ ,  $\text{CH}_2\text{-CO}$ ); 2.23 (3H, s,  $\text{CH}_3$ ); 2.14 (3H, s,  $\text{CH}_3$ );  $^{13}\text{C}$  NMR ( $\delta$ , ppm): 169.01( $\text{C}^6$ ); 168.90( $\text{COOMe}$ ); 168.63 ( $\text{C}^1$ ); 158.56 ( $\text{CONH}$ ); 134.14 ( $\text{C}^1$ ); 133.65( $\text{C}^4$ ); 129.85 ( $\text{C}^{9a}$ ); 126.68 ( $\text{C}^{3'}$ ,  $\text{C}^{5'}$ ); 125.10 ( $\text{C}^{2'}$ ,  $\text{C}^{6'}$ ); 116.84 ( $\text{C}^9$ ); 51.83 ( $\text{OCH}_3$ ); 38.68 ( $\text{C}^8$ ); 38.20 ( $\text{C}^3$ ); 35.65 ( $\text{CH}_2\text{-CO}$ ); 35.50 ( $\text{C}^7$ ); 27.69 ( $\text{C}^4$ ); 20.44 ( $\text{CH}_3$ ); 17.72 ( $\text{CH}_3$ ); HRMS (ESI): Found,  $m/z$  386.1714  $[\text{M}+\text{H}]^+$ .  $\text{C}_{20}\text{H}_{23}\text{N}_3\text{O}_5$  Calculated,  $[\text{M}+\text{H}]$  386.1712.

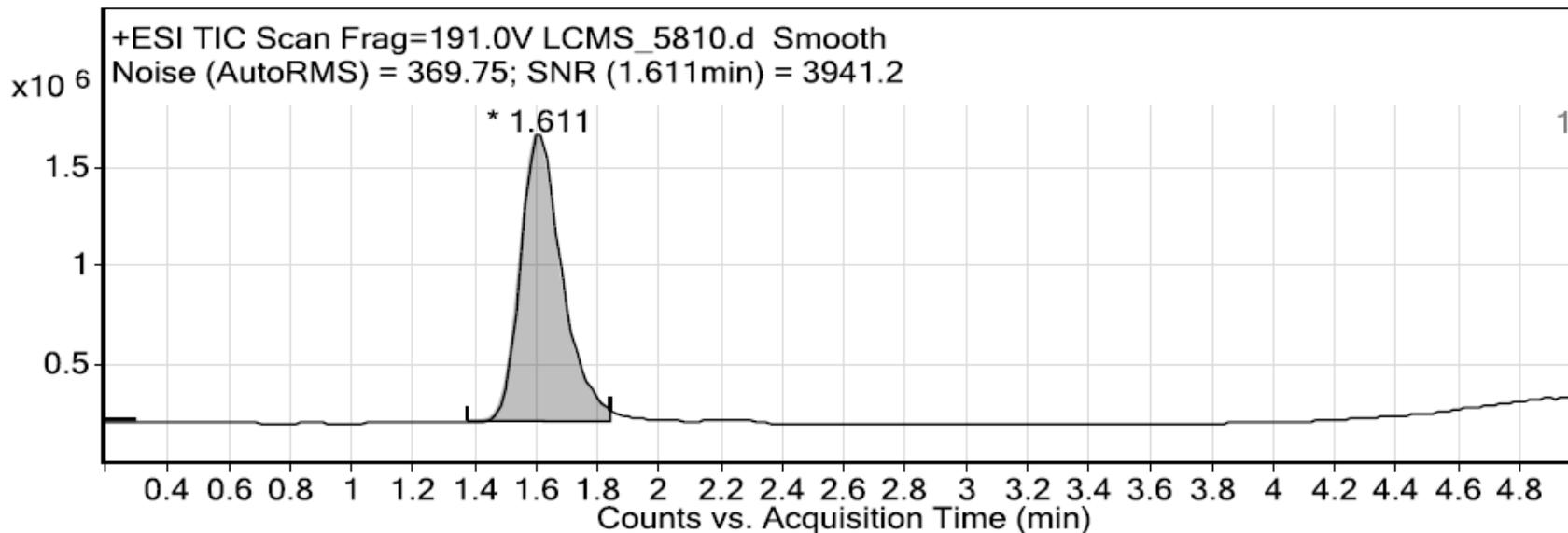




Data File LCMS\_5810.d Sample Name  
 Sample Type Sample Position Vial 21  
 Instrument Name Instrument 1 User Name  
 Acq Method ACN-H2O\_60-40.m Acquired Time 18-Nov-19 3:07:04 PM  
 IRM Calibration Status Success DA Method 13032017.m  
 Comment

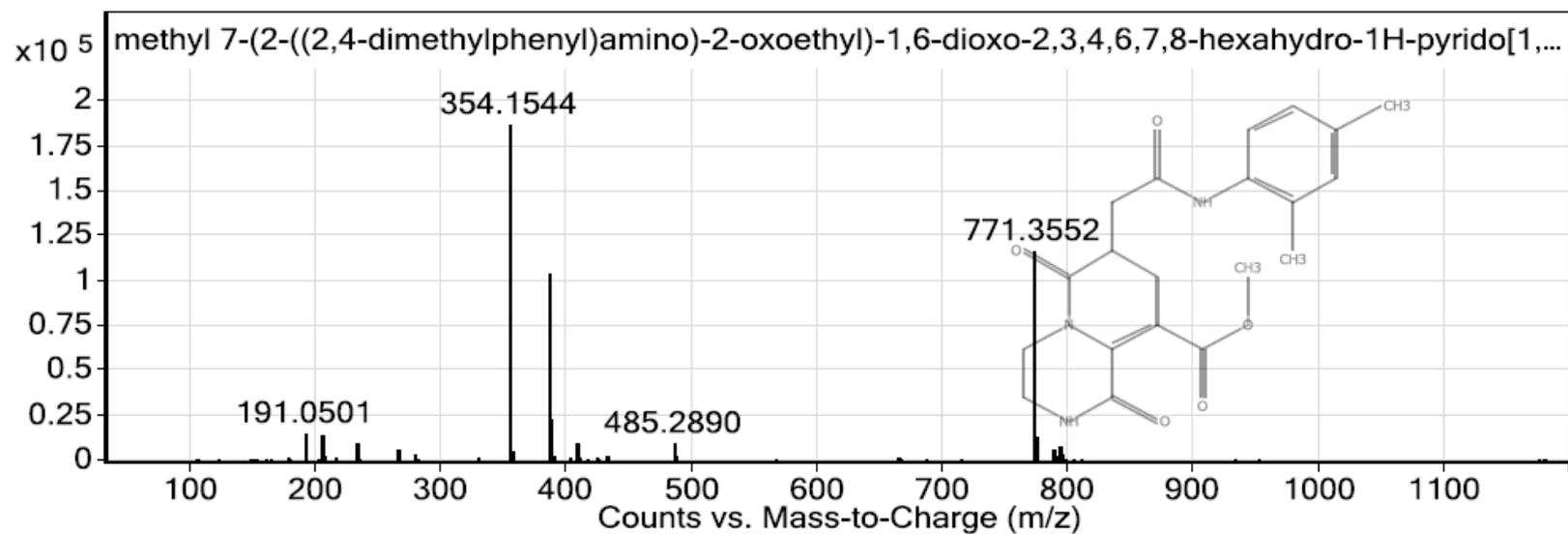
Sample Group Info.  
 Stream Name LC 1 Acquisition SW 6200 series TOF/6500 series  
 Version Q-TOF B.06.01 (B6157)

Fragmentor Voltage 191 Collision Energy 0 Ionization Mode ESI



User Chromatogram Peak List

RT	Height	Height %	Area	Area %	Area Sum %	S/N	Symmetry	Width
1.611	1457256.09	100	14028033.58	100	100	3941.2	1.45	0.464

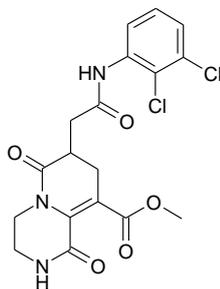


MS Spectrum Peak List

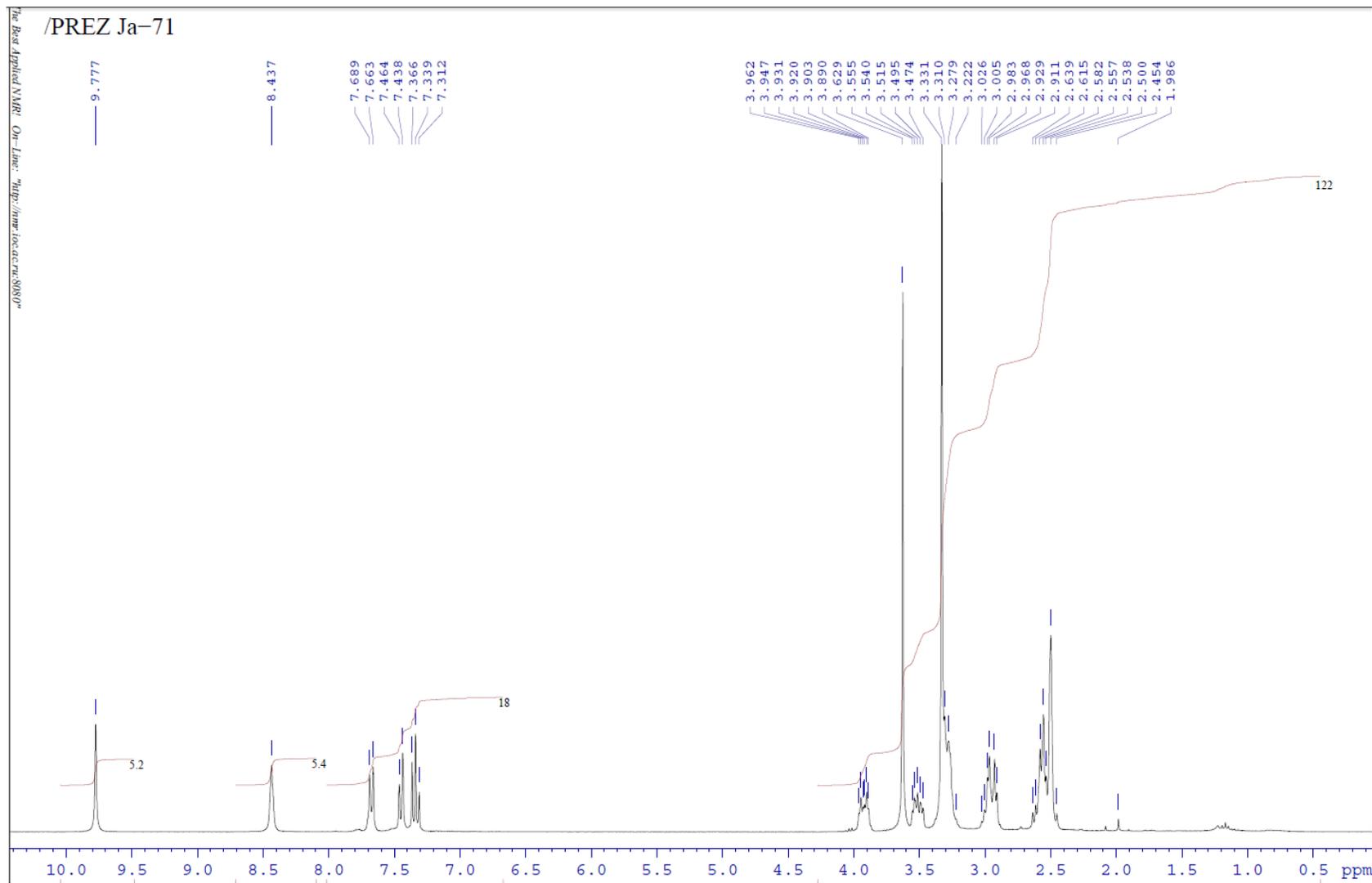
m/z	z	Abund
191.0501		15145.66
205.0663		14391.09
233.0618		10246.51
354.1544	1	187285.27
355.1575	1	38469.61
386.1714	1	104688.32
387.1846	1	22999.57
771.3552	1	116743.27
772.3583	1	51891.3
773.3611	1	13684.08

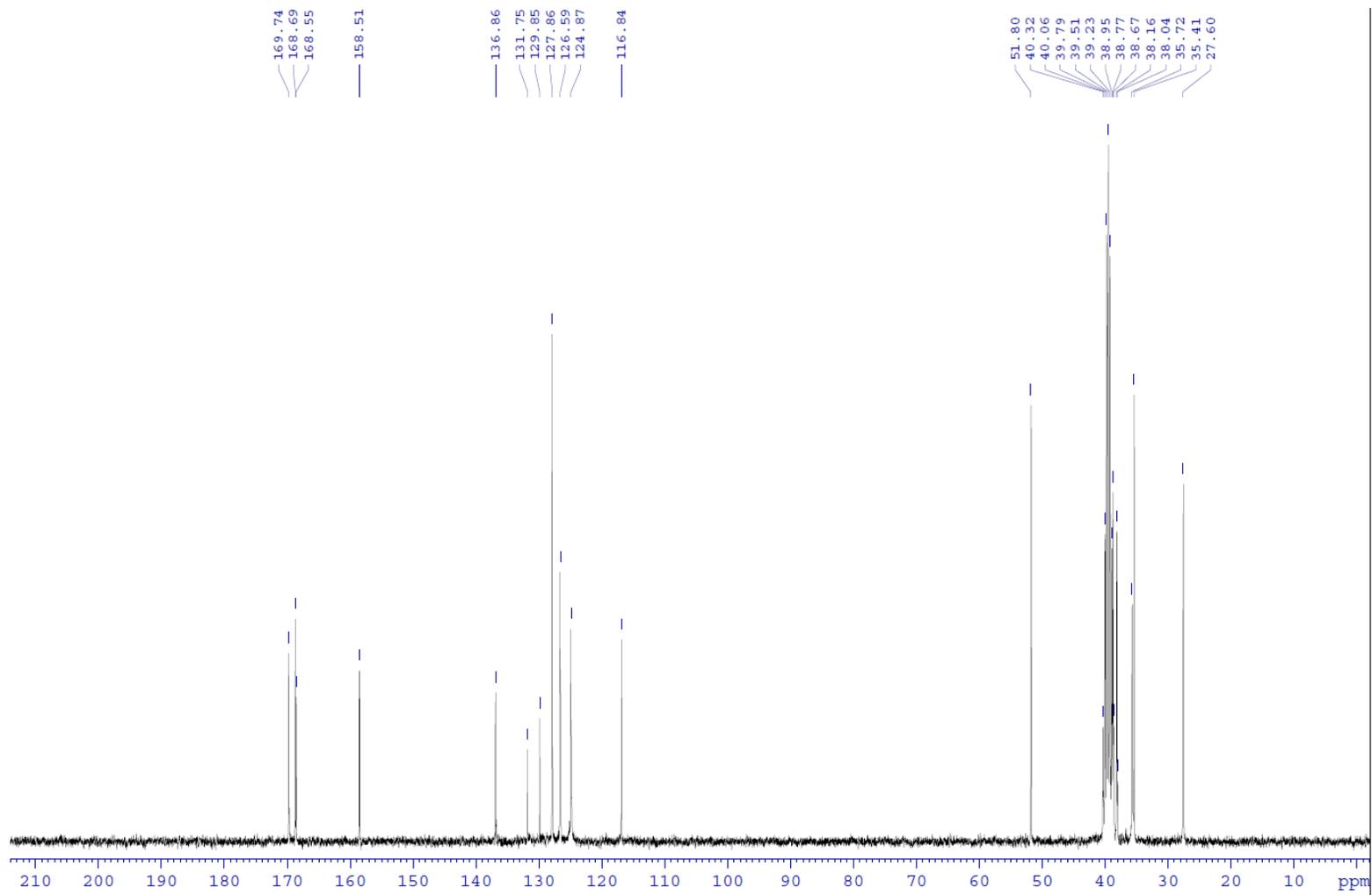
**Methyl 7-[2-(2,3-dichlorophenylamino)-2-oxoethyl]-1,6-dioxo-1,3,4,6,7,8-hexahydro-2H-pyrido[1,2-a]pyrazine-9-carboxylate (3d).**

Yield: 1.34 g (63%), powdery compound, light beige, m.p. 235-236 °C.



$^1\text{H}$  NMR, (( $\delta$ , ppm.,  $J/\text{Hz}$ ): 9.77 (1H, s, NH) 8.43 (1H, s, NH); 7.69-7.31 (3H, m, Ar); 3.96-3.89 (1H, m,  $\text{CH}_2^8$ ); 3.62 (3H, s, O- $\text{CH}_3$ ) 3.55-3.47 (1H, m,  $\text{CH}_2^8$ ); 3.31-3.27 (2H, m,  $\text{CH}_2^3$ ); 3.02-2.91 (2H, m, 1H, - $\text{CH}^7$ +1H,  $\text{CH}_2$ -CO); 2.63-2.45 (3H, m, 2H  $\text{CH}_2^4$ +1H,  $\text{CH}_2$ -CO);  $^{13}\text{C}$  NMR ( $\delta$ , ppm): 169.74 ( $\text{COOMe}$ ); 168.69( $\text{C}^6$ ); 168.55 ( $\text{C}^1$ ); 158.51( $\text{CONH}$ ); 136.86 ( $\text{C}^{1'}$ ); 131.75 ( $\text{C}^{4'}$ ); 129.85 ( $\text{C}^{9a}$ ); 127.86 ( $\text{C}^{3'}$ ,  $\text{C}^{5'}$ ); 126.59 ( $\text{C}^{2'}$ ); 124.87 ( $\text{C}^{6'}$ ); 116.84 ( $\text{C}^9$ ); 51.80 ( $\text{OCH}_3$ ); 38.67 ( $\text{C}^8$ ); 38.04 ( $\text{C}^3$ ); 35.72 ( $\text{CH}_2$ -CO); 35.41 ( $\text{C}^7$ ); 27.60 ( $\text{C}^4$ ); HRMS (ESI): Found,  $m/z$ , 426.0613  $[\text{M}+\text{H}]^+$ .  $\text{C}_{18}\text{H}_{17}\text{Cl}_2\text{N}_3\text{O}_5$  Calculated,  $[\text{M}+\text{H}]$  426.0619.

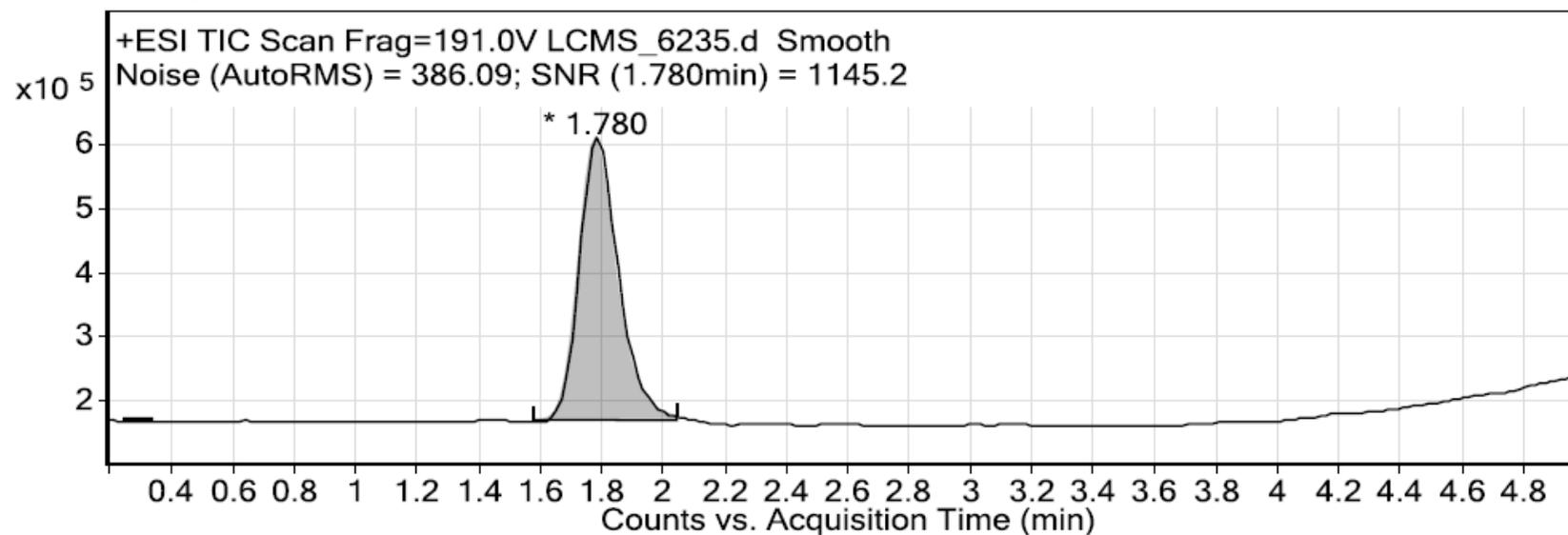




**Data File** LCMS\_6235.d      **Sample Name**  
**Sample Type** Sample      **Position** Vial 36  
**Instrument Name** Instrument 1      **User Name**  
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**IRM Calibration Status** Success      **DA Method** 13032017.m  
**Comment**

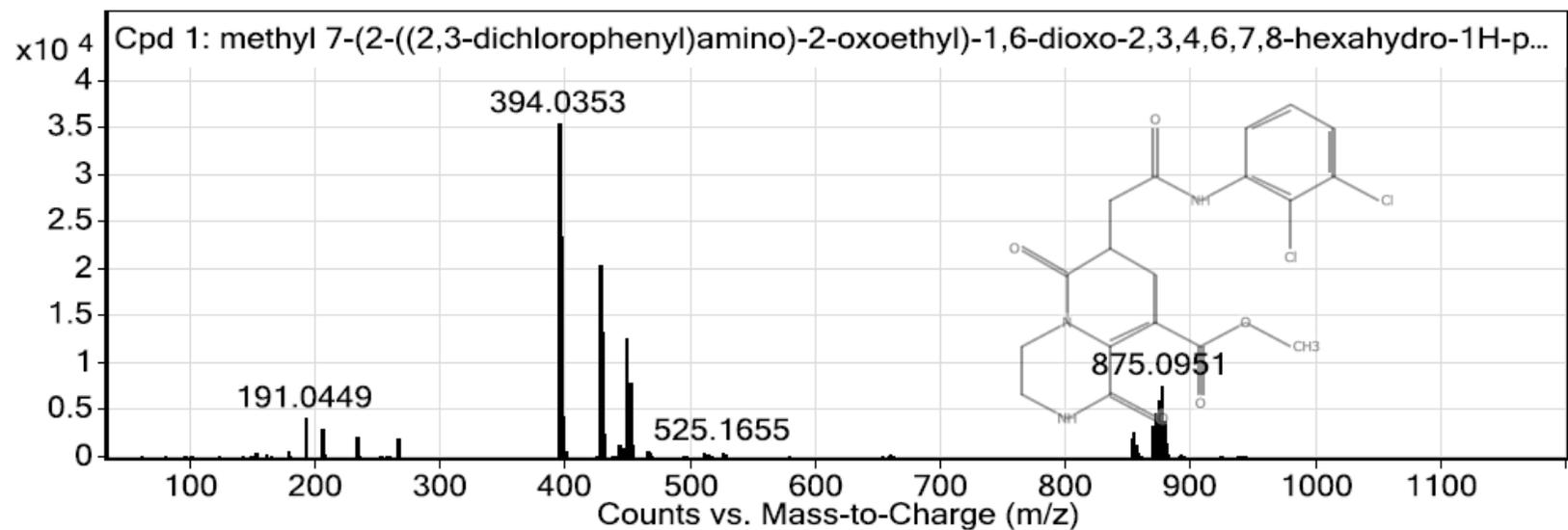
**Sample Group** Info.  
**Stream Name** LC 1      **Acquisition SW** 6200 series TOF/6500 series  
**Version** Q-TOF B.06.01 (B6157)

**Fragmentor Voltage** 191    **Collision Energy** 0    **Ionization Mode** ESI



**User Chromatogram Peak List**

RT	Height	Height %	Area	Area %	Area Sum %	S/N	Symmetry	Width
1.78	442149.99	100	3990127.14	100	100	1145.2	1.42	0.464



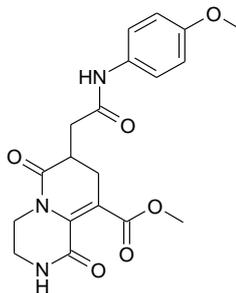
**MS Spectrum Peak List**

<i>m/z</i>	<i>z</i>	Abund
394.0353	1	35510.72
395.0382	1	7025
396.0323	1	23508.16
426.0613	1	20340.34
428.0591	1	13361.72
448.0432	1	12759.89
450.0407	1	8158.47
870.1392	1	4848.54
873.1021	1	6057.09
875.0951	1	7667.97

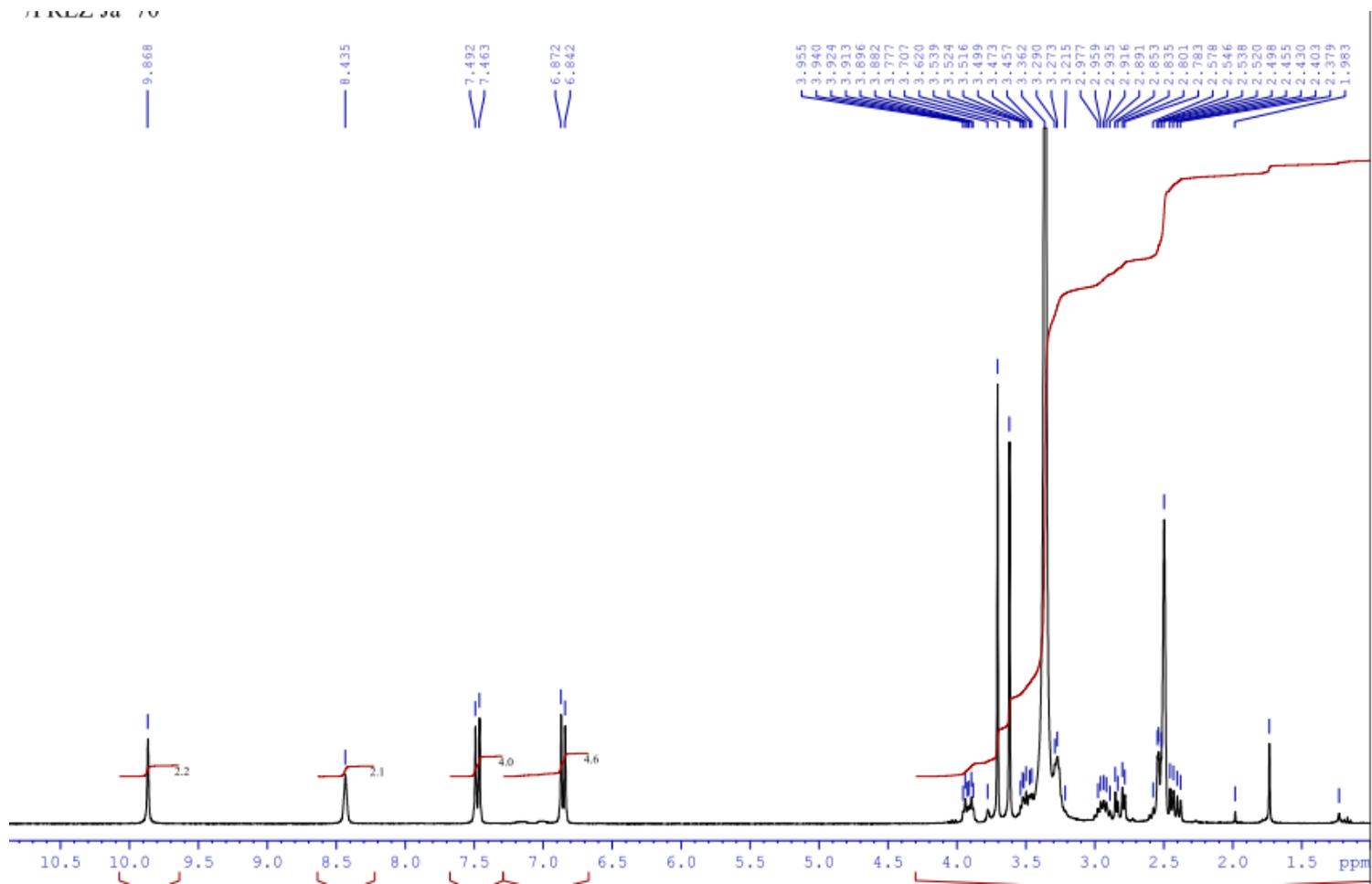
**Compound Structure**

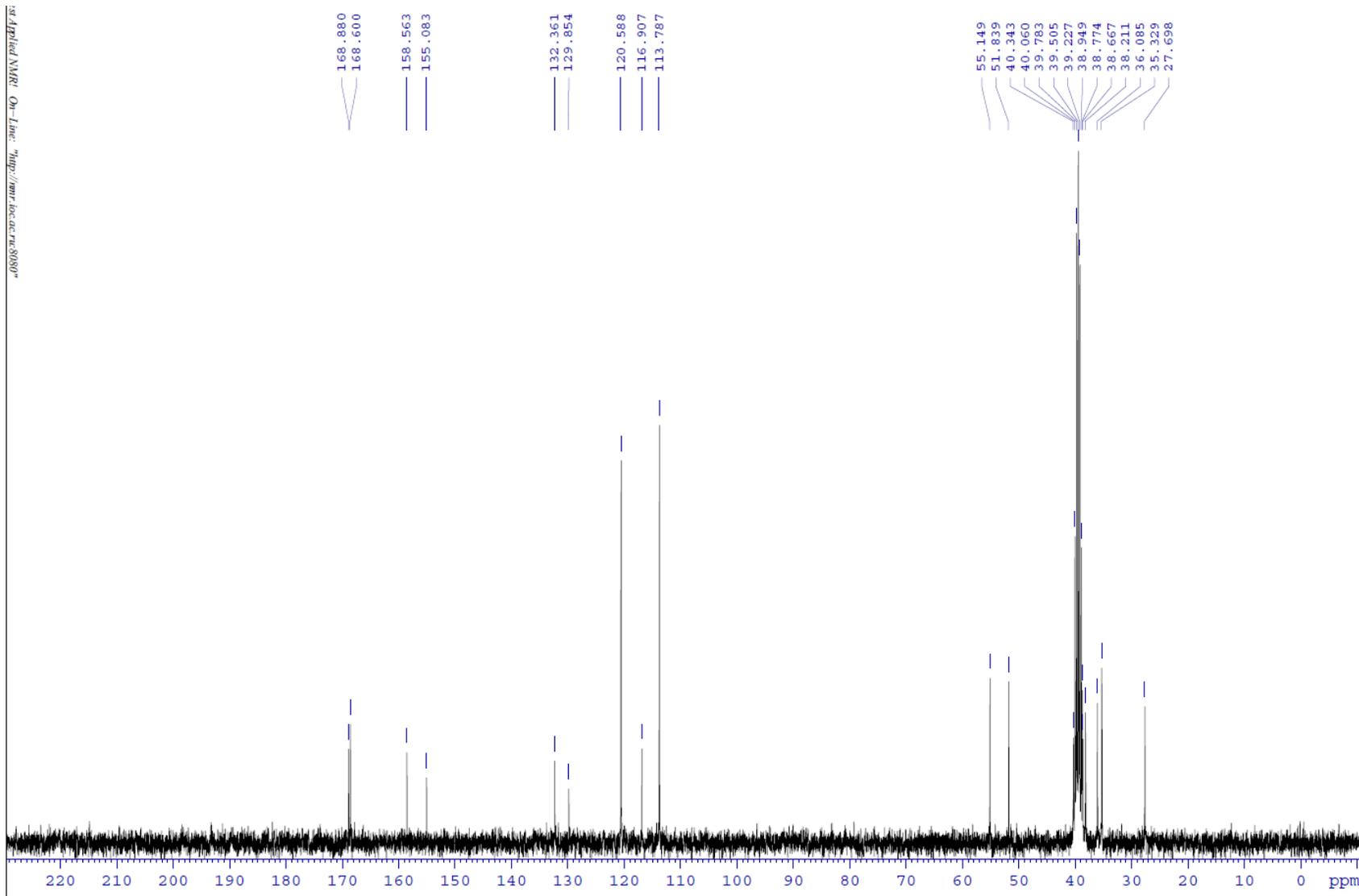
**Methyl 7-[2-(4-methoxyphenylamino)-2-oxoethyl]-1,6-dioxo-1,3,4,6,7,8-hexahydro-2H-pyrido[1,2-a]pyrazine-9-carboxylate (3e).**

Yield: 1.16 g (40%), white powder compound, m.p. 230-231 ° C.



$^1\text{H}$  NMR, ( $\delta$ , ppm.,  $J/\text{Hz}$ ): 9.87 (1H s, NH); 8.43 (1H, s, NH); 7.49-6.84 (3H, m, Ar); 3.95-3.88 (1H, m,  $\text{CH}_2^8$ ); 3.62 (3H, s, O- $\text{CH}_3$ ); 3.54 (3H, s, O- $\text{CH}_3(\text{Ar})$ ); 3.54-3.51 (1H, m,  $\text{CH}_2^8$ ); 3.29-3.26 (2H, m,  $\text{CH}_2^3$ ); 2.97-2.89 (1H, m, - $\text{CH}^7$ ); 2.87 (1H, dd,  $J_1 = 15.6$ ,  $J_2 = 5.4$ ,  $\text{CH}_2\text{-CO}$ ); 2.57-2.53 (2H, m,  $\text{CH}_2^4$ ); 2.41 (1H dd,  $J_1 = 15.6$ ,  $J_2 = 7.5$ ,  $\text{CH}_2\text{-CO}$ );  $^{13}\text{C}$  NMR ( $\delta$ , ppm): 168.88 ( $\text{COOMe}$ ); 168.60 ( $\text{C}^6$ ); 158.56 ( $\text{C}^1$ ); 155.08 ( $\text{CONH}$ ); 132.36 ( $\text{C}^4$ ,  $\text{C}^{1'}$ ); 129.85 ( $\text{C}^{9a}$ ); 120.58 ( $\text{C}^{3'}$ ,  $\text{C}^{5'}$ ); 116.90 ( $\text{C}^9$ ); 113.78 ( $\text{C}^2$ ,  $\text{C}^6$ ); 55.14 (O- $\text{CH}_3(\text{Ar})$ ); 51.83 (O- $\text{CH}_3$ ); 38.21 ( $\text{C}^8$ ); 38.21 ( $\text{C}^3$ ); 36.08 ( $\text{CH}_2\text{-CO}$ ); 35.32 ( $\text{C}^7$ ); 27.69 ( $\text{C}^4$ ); HRMS (ESI): Found,  $m/z$  388.15045 [ $\text{M}+\text{H}$ ] $^+$ .  $\text{C}_{19}\text{H}_{21}\text{N}_3\text{O}_6$  Calculated, [ $\text{M}+\text{H}$ ] 388.15044.

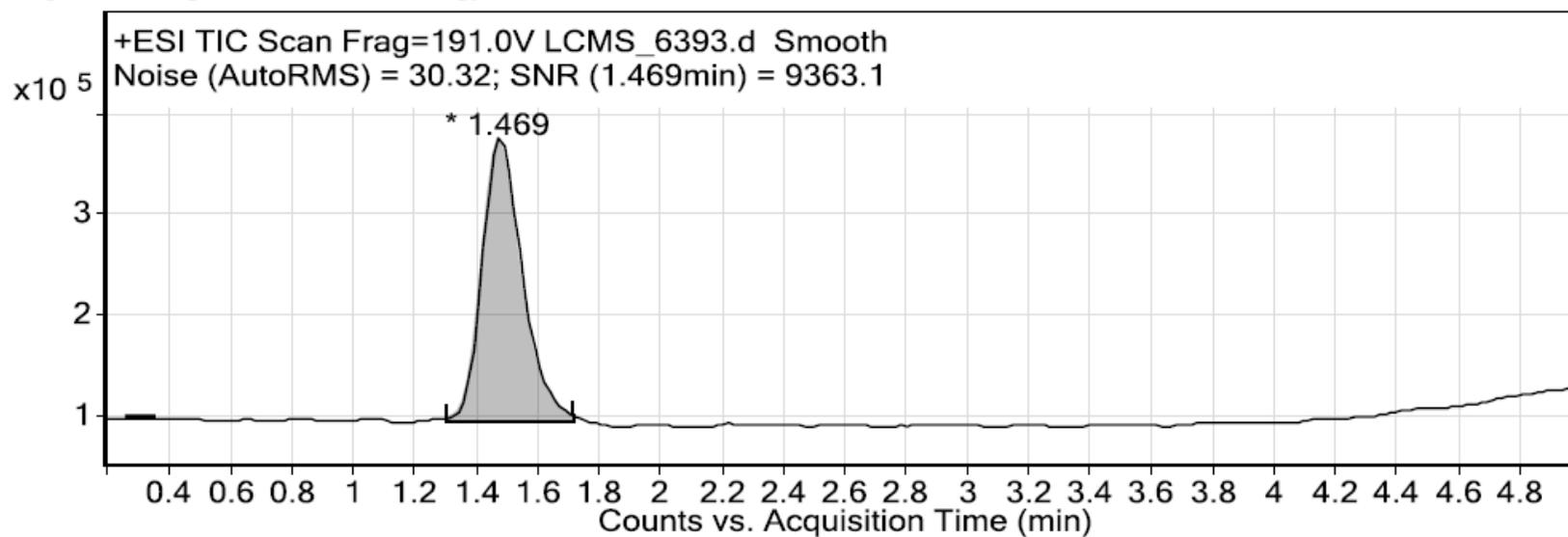




**Data File** LCMS\_6393.d **Sample Name**  
**Sample Type** Sample **Position** Vial 22  
**Instrument Name** Instrument 1 **User Name**  
**Acq Method** ACN-H2O\_60-40.m **Acquired Time** 28-Feb-20 2:32:56 PM  
**IRM Calibration Status** Success **DA Method** 13032017.m  
**Comment**

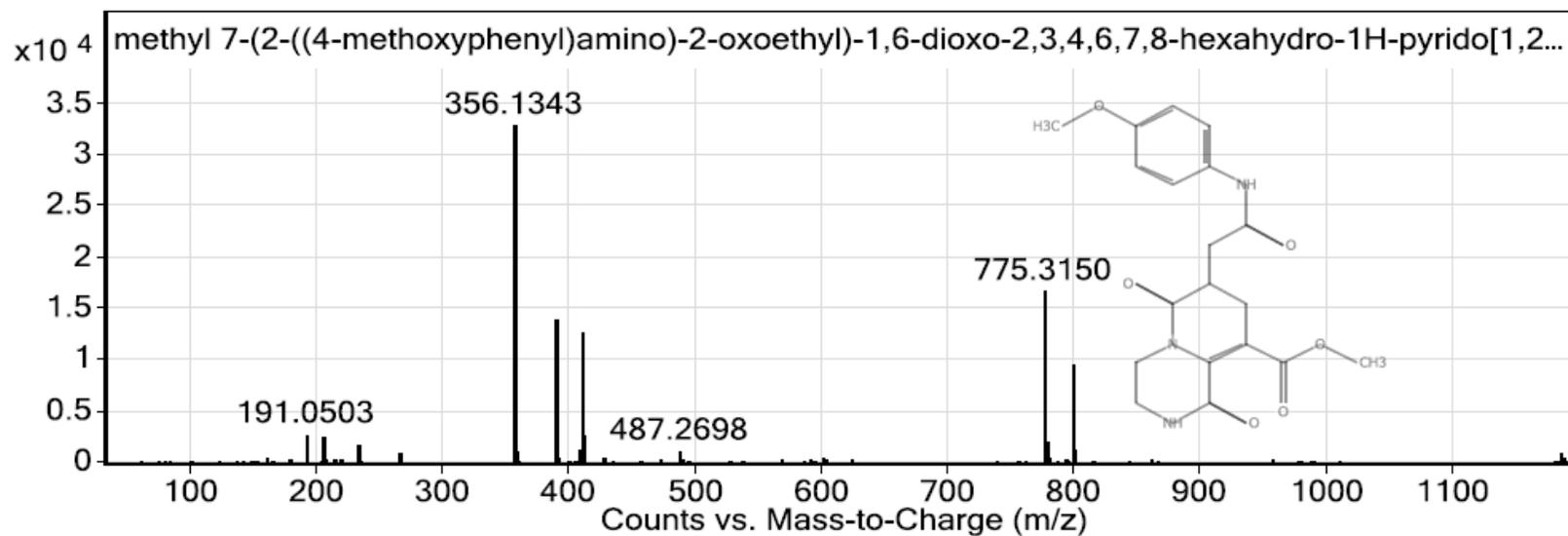
**Sample Group** Info.  
**Stream Name** LC 1 **Acquisition SW** 6200 series TOF/6500 series  
**Version** Q-TOF B.06.01 (B6157)

**Fragmentor Voltage** 191 **Collision Energy** 0 **Ionization Mode** ESI



**User Chromatogram Peak List**

RT	Height	Height %	Area	Area %	Area Sum %	S/N	Symmetry	Width
1.469	283859.56	100	2653039.33	100	100	9363.1	1.57	0.414



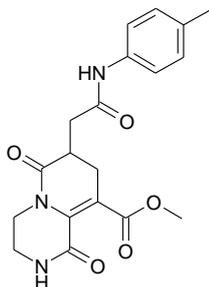
MS Spectrum Peak List

m/z	z	Abund
356.1343	1	33010.72
357.1378	1	6668.72
388.1504	1	14116.65
389.1658	1	3200.56
410.1441	1	12914.75
411.1474	1	2855.27
775.315	1	16787.54
776.3188	1	7479.19
797.2976	1	9642.77
798.3005	1	4430.86

Compound Structure

**Methyl 7-[2-(4-methylphenylamino)-2-oxoethyl]-1,6-dioxo-1,3,4,6,7,8-hexahydro-2H-pyrido[1,2-a]pyrazin-9-carboxylate (3f).**

Yield: 1.25 g (67%), white powdery compound, m.p. 228-229 °C



$^1\text{H}$  NMR, ( $\delta$ , ppm.,  $J/\text{Hz}$ ): 9.91 (1H, s, NH); 8.44 (1H, s, NH); 6.46-7.08 (3H, m, Ar); 3.94-3.90 (1H, m,  $\text{CH}_2^8$ ); 3.62 (3H s, O- $\text{CH}_3$ ); 3.51-3.47 (1H, m,  $\text{CH}_2^8$ ); 3.29-3.26 (2H, m,  $\text{CH}_2^3$ ); 2.98-2.92 (1H, m,  $\text{CH}^7$ ); 2.83 (1H, dd,  $J_1 = 12.00$ ,  $J_2 = 6.00$ ,  $\text{CH}_2\text{-CO}$ ); 2.57-2.51 (2H, m,  $\text{CH}_2^4$ ); 2.44 (1H dd,  $J_1 = 18.00$ ,  $J_2 = 6.00$   $\text{CH}_2\text{-CO}$ ); 2.23 (3H, m,  $\text{CH}_3$  (Ar));  $^{13}\text{C}$  NMR ( $\delta$ , ppm): 168.87 ( $\text{COOMe}$ ,  $\text{C}^6$ ); 168.62 ( $\text{C}^1$ ); 158.55 ( $\text{CONH}$ ); 136.67 ( $\text{C}^{1'}$ ); 131.91 ( $\text{C}^{4'}$ ); 129.84 ( $\text{C}^{9a}$ ); 129.01 ( $\text{C}^{3'}$ ,  $\text{C}^{5'}$ ); 119.04 ( $\text{C}^{2'}$ ,  $\text{C}^{6'}$ ); 116.92 ( $\text{C}^9$ ); 51.83 ( $\text{OCH}_3$ ); 38.76 ( $\text{C}^8$ ); 38.20 ( $\text{C}^3$ ); 36.16 ( $\text{CH}_2\text{-CO}$ ); 35.28 ( $\text{C}^7$ ); 27.69 ( $\text{C}^4$ ); 20.40 ( $\text{CH}_3$ ); HRMS (ESI): Found,  $m/z$  372.1558 [ $\text{M}+\text{H}$ ] $^+$ .  $\text{C}_{19}\text{H}_{21}\text{N}_3\text{O}_5$  Calculated, [ $\text{M}+\text{H}$ ] 372,1555.

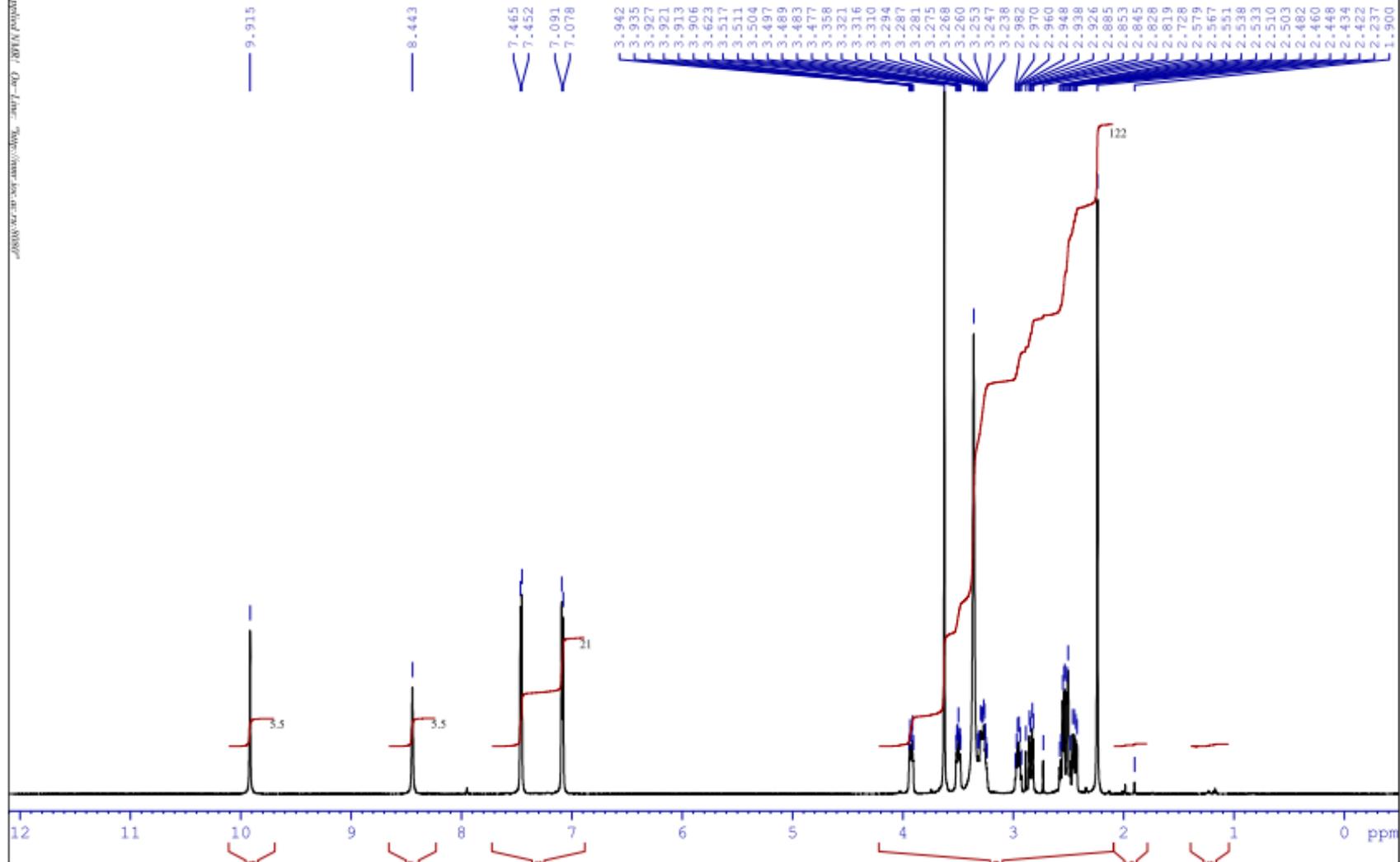
Correlations and coordinates of cross-peaks in the NOESY  $^1\text{H}$ - $^1\text{H}$  spectrum.

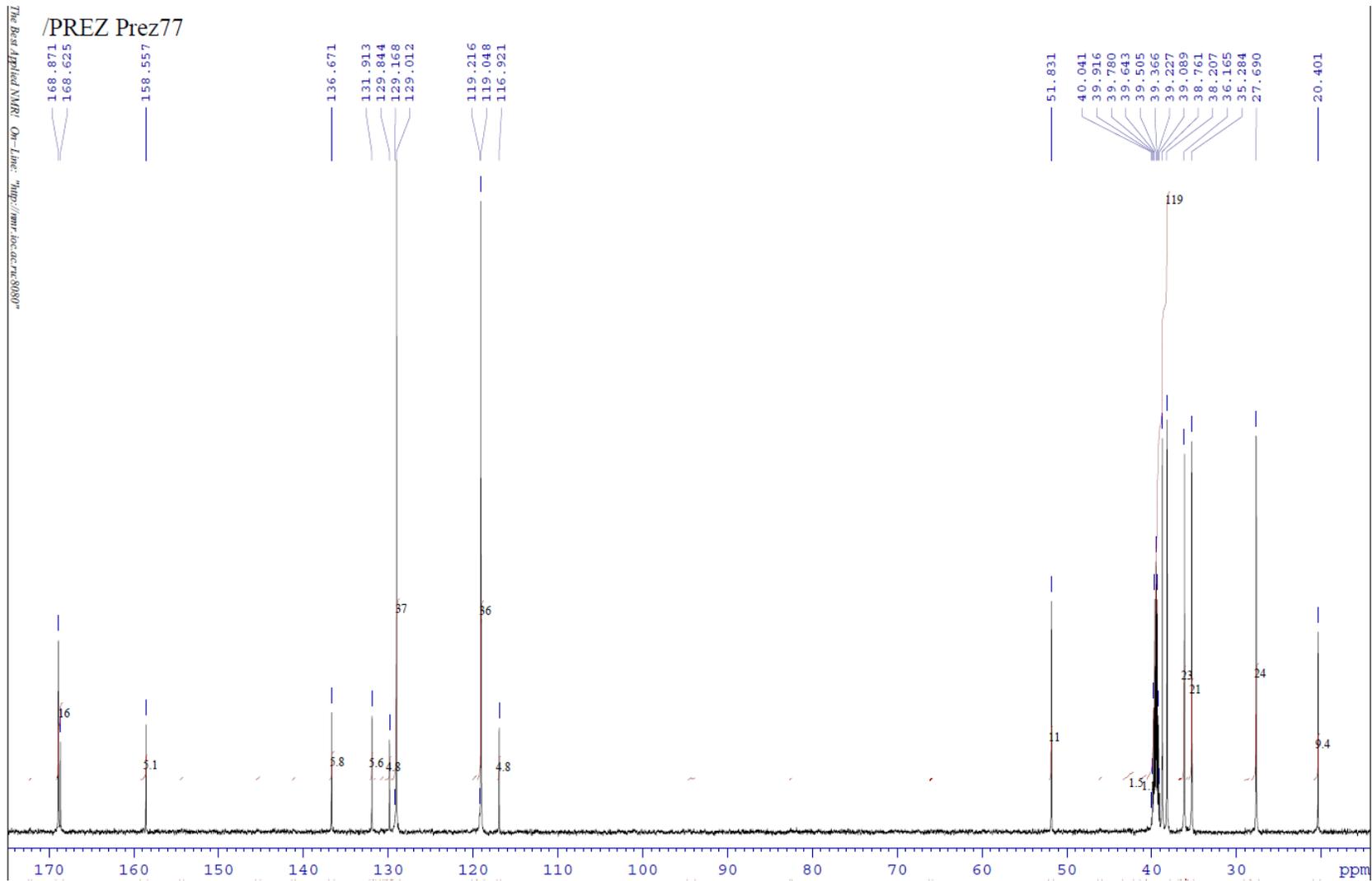
Protons ( $\delta$ , ppm)	Interacting protons ( $\delta$ , ppm)
$\text{CH}_2$ exo (2.44)	$\text{CH}_2$ exo (2.83), 2.92 ( $\text{CH}^7$ );
$\text{CH}_2^4$ (2.59)	$\text{CH}_2^3$ (3.27)
$\text{CH}_2$ exo (2.83),	$\text{CH}_2$ exo (2.44), $\text{CH}^7$ (2.92);
$\text{CH}^7$ (2.92);	$\text{CH}_2$ exo (2.44), $\text{CH}_2$ exo (2.83),
$\text{CH}_2^3$ (3.27)	$\text{CH}_2^4$ (2.59)
$\text{CH}_2^8$ (3.50 );	$\text{CH}_2^8$ (3.92 );
$\text{CH}_2^8$ (3.92 );	$\text{CH}_2^8$ (3.50 );
2CH-Ar (7.09)	2CH-Ar (7.45)
2CH-Ar (7.45)	2CH-Ar (7.09), $\text{NH}$ (9.91)
$\text{NH}$ (9.91)	2CH-Ar (7.09)

Correlations and coordinates of cross-peaks in the HMBC  $^1\text{H}$ - $^{13}\text{C}$  spectrum .

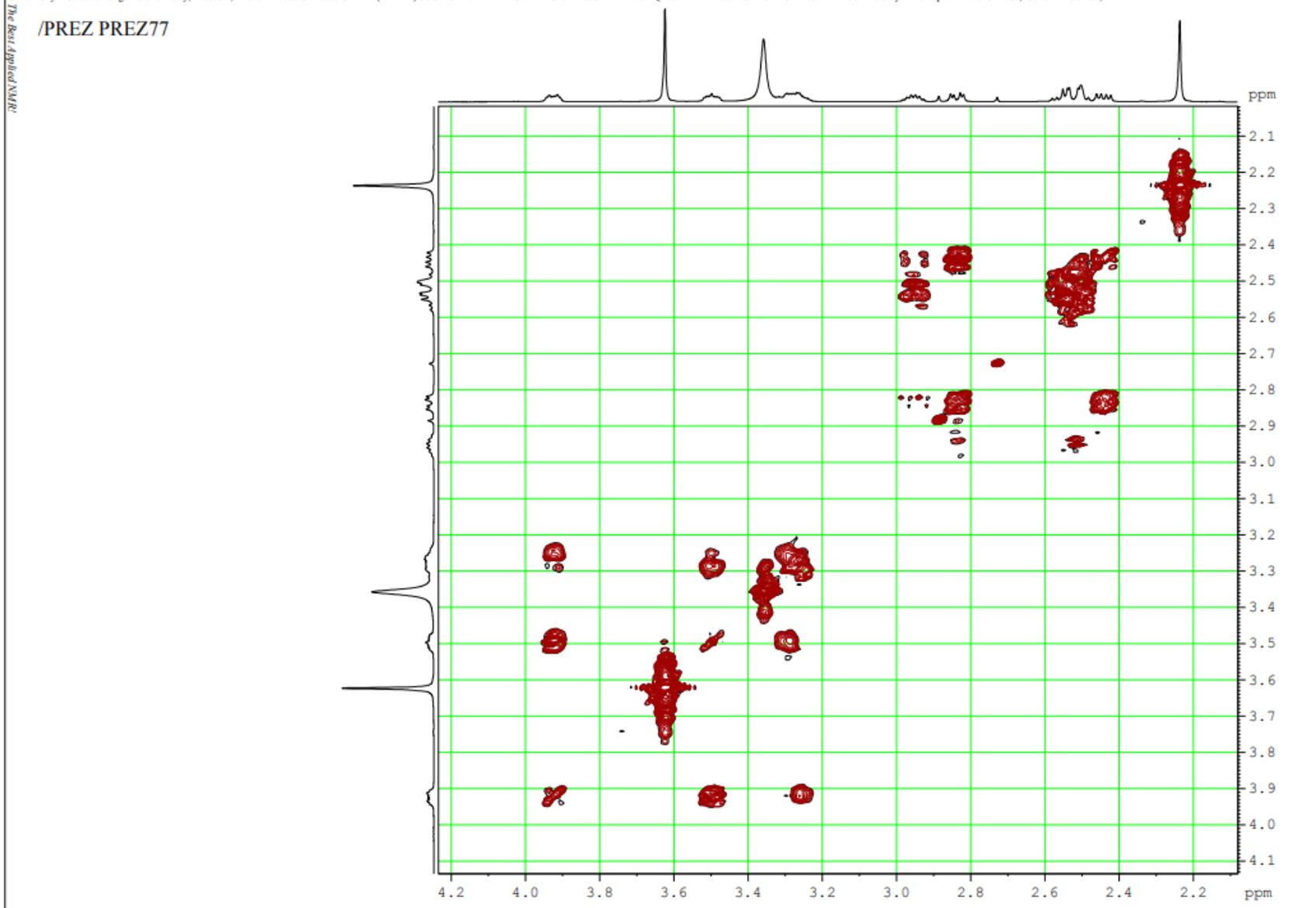
Protons ( $\delta$ , m.d.)	Atoms $^{13}\text{C}$ ( $\delta$ , ppm)
$\text{CH}_3$ Ar (2.23);	$\text{C}^{4'}$ (131.91); $\text{C}^{3'}$ , $\text{C}^{5'}$ (129.01);
$\text{CH}_2$ exo (2.44)	$\text{CONH}$ (158.55);
$\text{CH}_2$ exo (2.83),	$\text{CONH}$ (158.55);
$\text{CH}^7$ (2.92);	$\text{CONH}$ (158.55);
O- $\text{CH}_3$ (3.62);	$\text{COOMe}$ (168.87);
$\text{NH}$ (8.44);	$\text{C}^1$ (168.62);
$\text{NH}$ (9.91)	$\text{C}^{2'}$ , $\text{C}^{6'}$ (119.04); $\text{CONH}$ (158.55);

/PREZ PREZ77

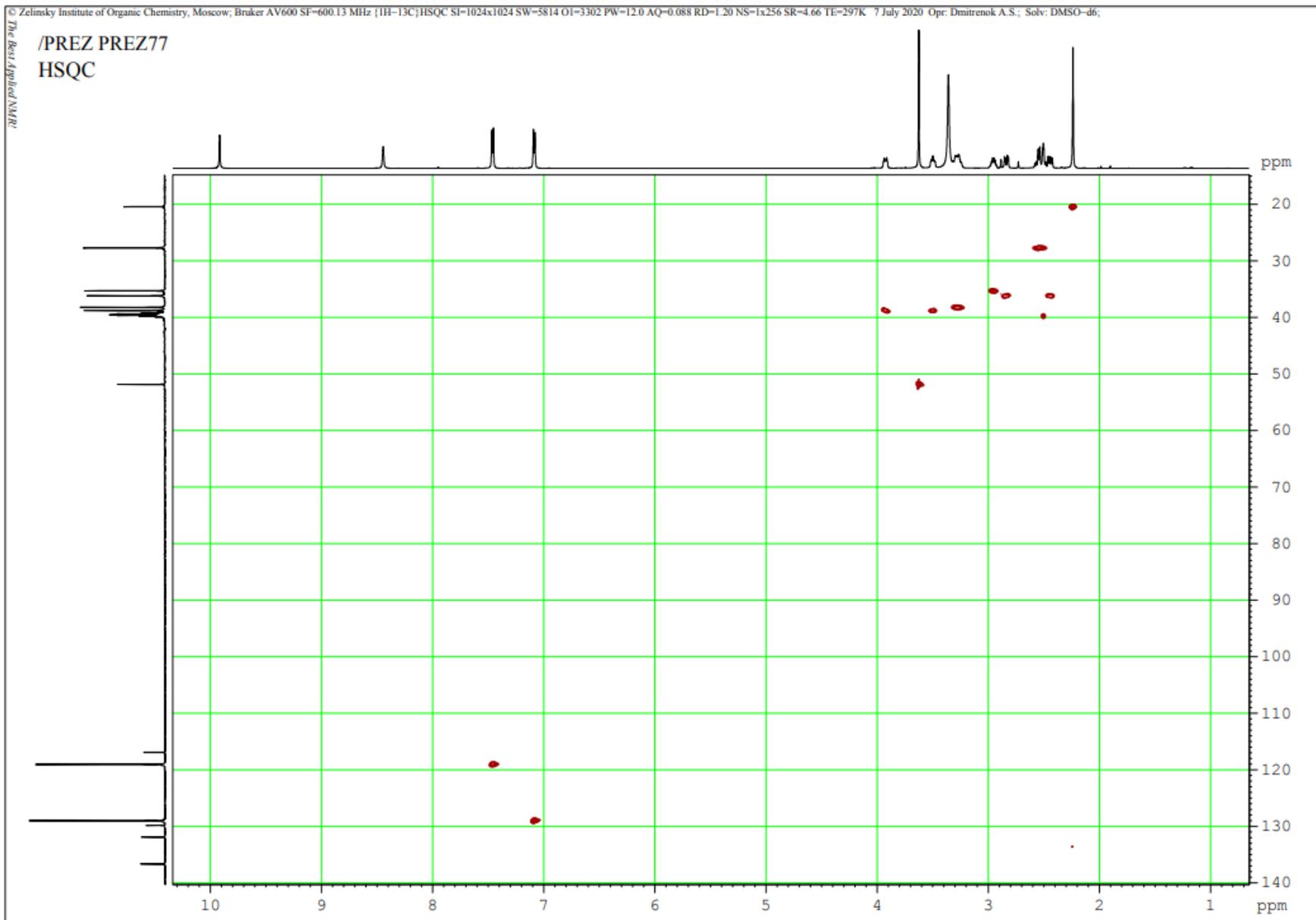




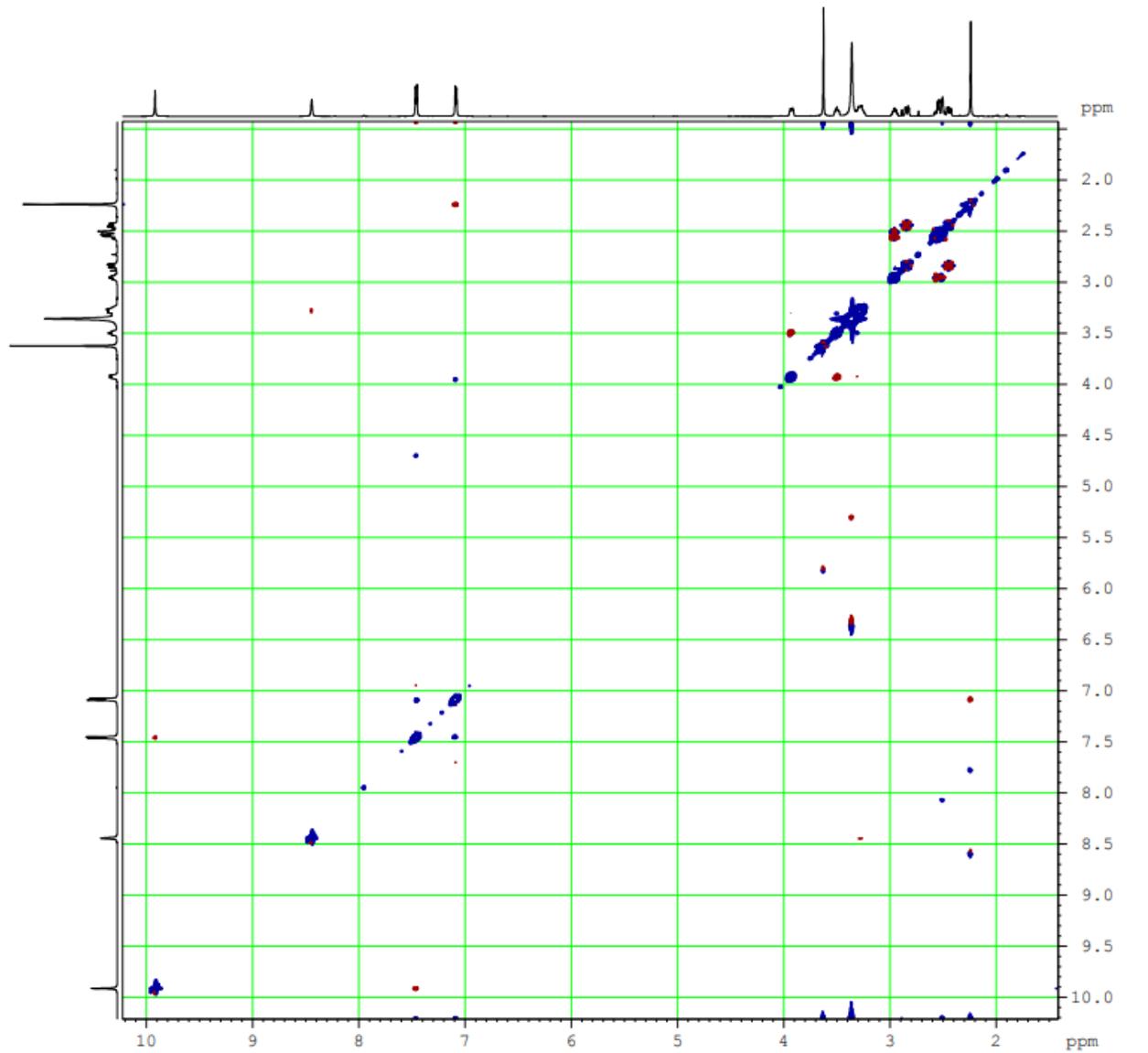
/PREZ PREZ77

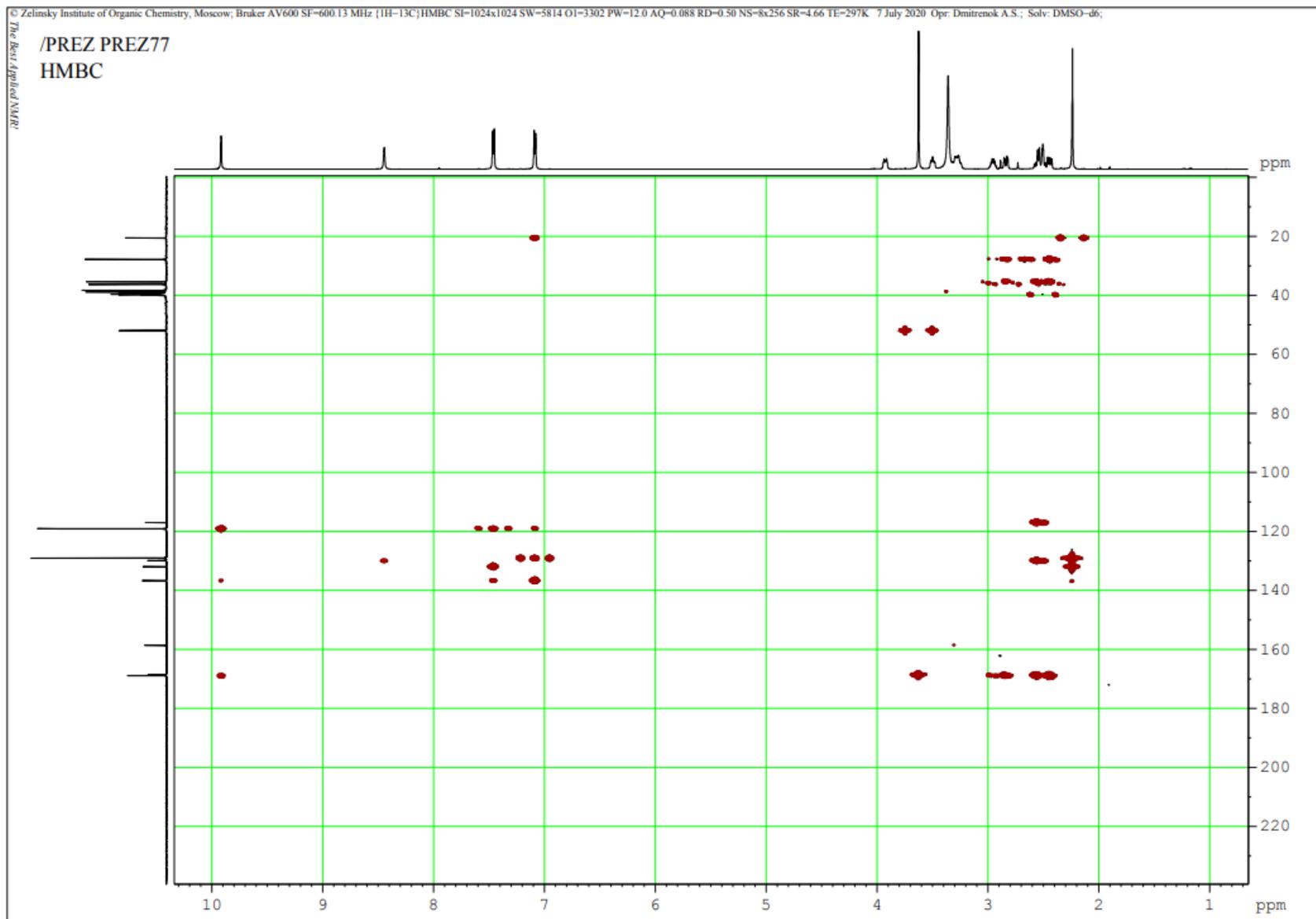


/PREZ PREZ77  
HSQC



/PREZ PREZ77

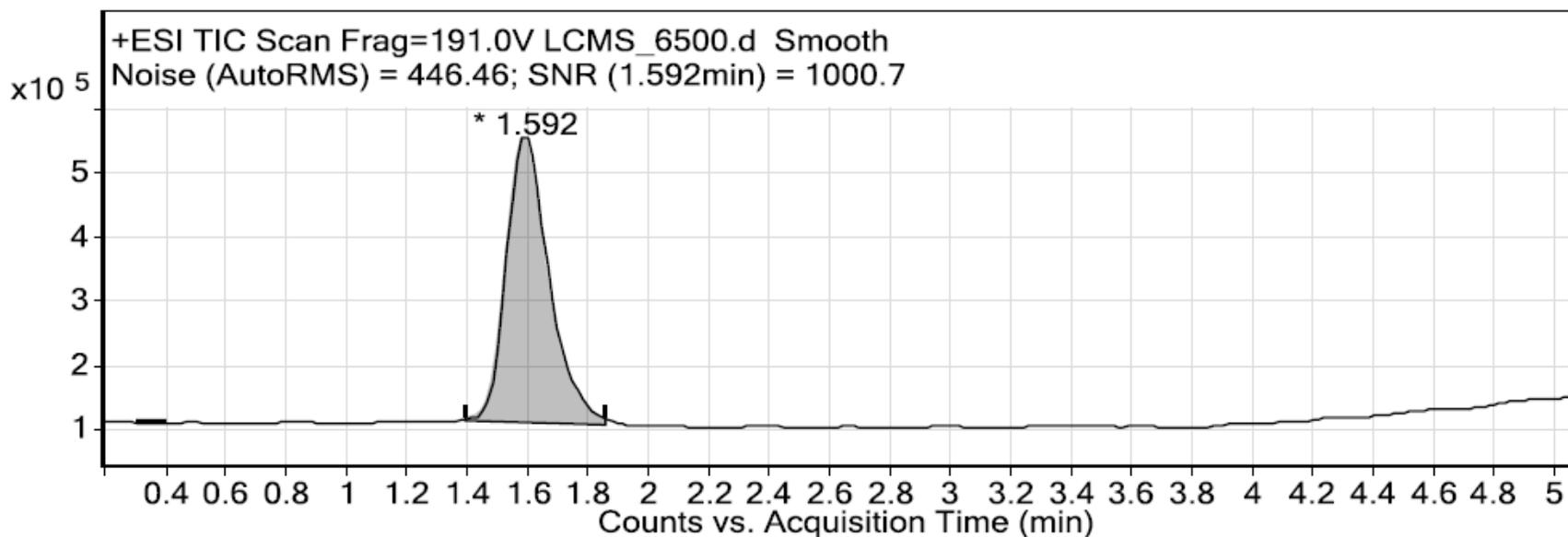




**Data File** LCMS\_6500.d      **Sample Name**  
**Sample Type** Sample      **Position** Vial 25  
**Instrument Name** Instrument 1      **User Name**  
**Acq Method** ACN-H2O\_60-40.m      **Acquired Time** 13-Mar-20 2:08:08 PM  
**IRM Calibration Status** Success      **DA Method** 13032017.m  
**Comment**

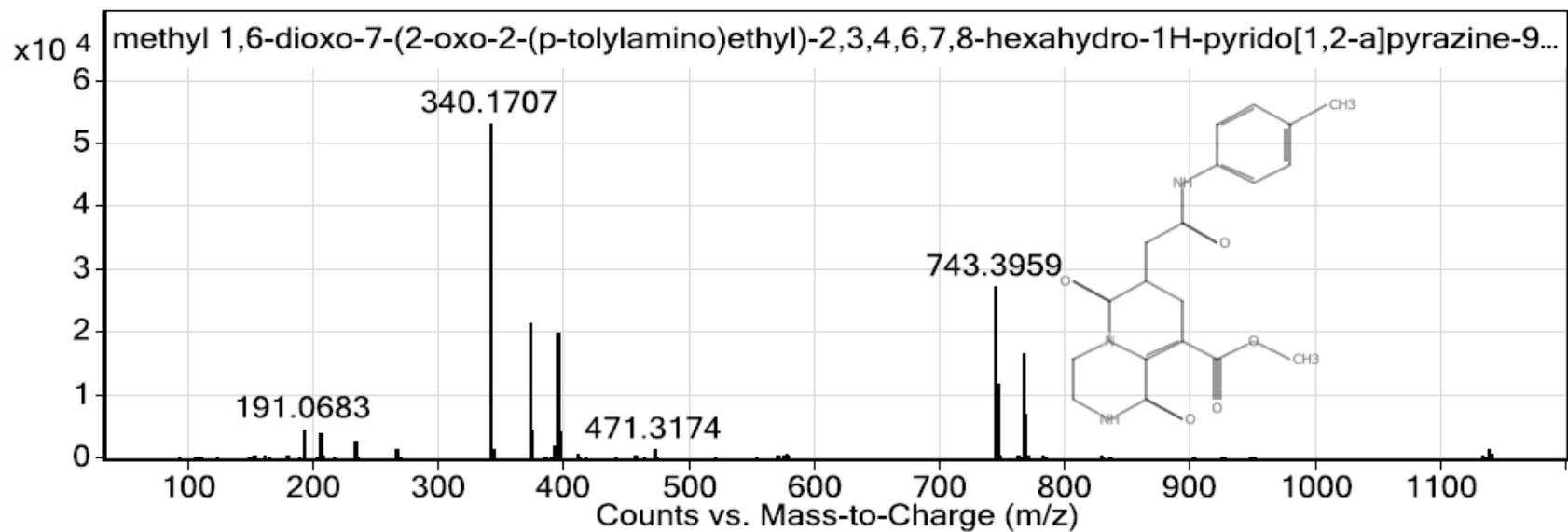
**Sample Group** Info.  
**Stream Name** LC 1      **Acquisition SW** 6200 series TOF/6500 series  
    **Version** Q-TOF B.06.01 (B6157)

**Fragmentor Voltage** 191    **Collision Energy** 0    **Ionization Mode** ESI



**User Chromatogram Peak List**

RT	Height	Height %	Area	Area %	Area Sum %	S/N	Symmetry	Width
1.592	446774.37	100	4509522.87	100	100	1000.7	1.38	0.464

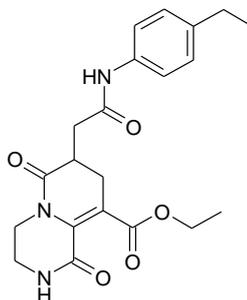


MS Spectrum Peak List

m/z	z	Abund
191.0683		4753.72
340.1707	1	53225.17
341.1742	1	10714.56
372.1558	1	21499.81
373.2048	1	4826.33
394.1854	1	20100.95
743.3959	1	27333.51
744.3987	1	12027.39
765.3802	1	16832.21
766.3837	1	7388.11

**Ethyl 7-[2-(4-ethylphenylamino)-2-oxoethyl]-1,6-dioxo-1,3,4,6,7,8-hexahydro-2H-pyrido-[1,2-a]pyrazine-9-carboxylate (3f).**

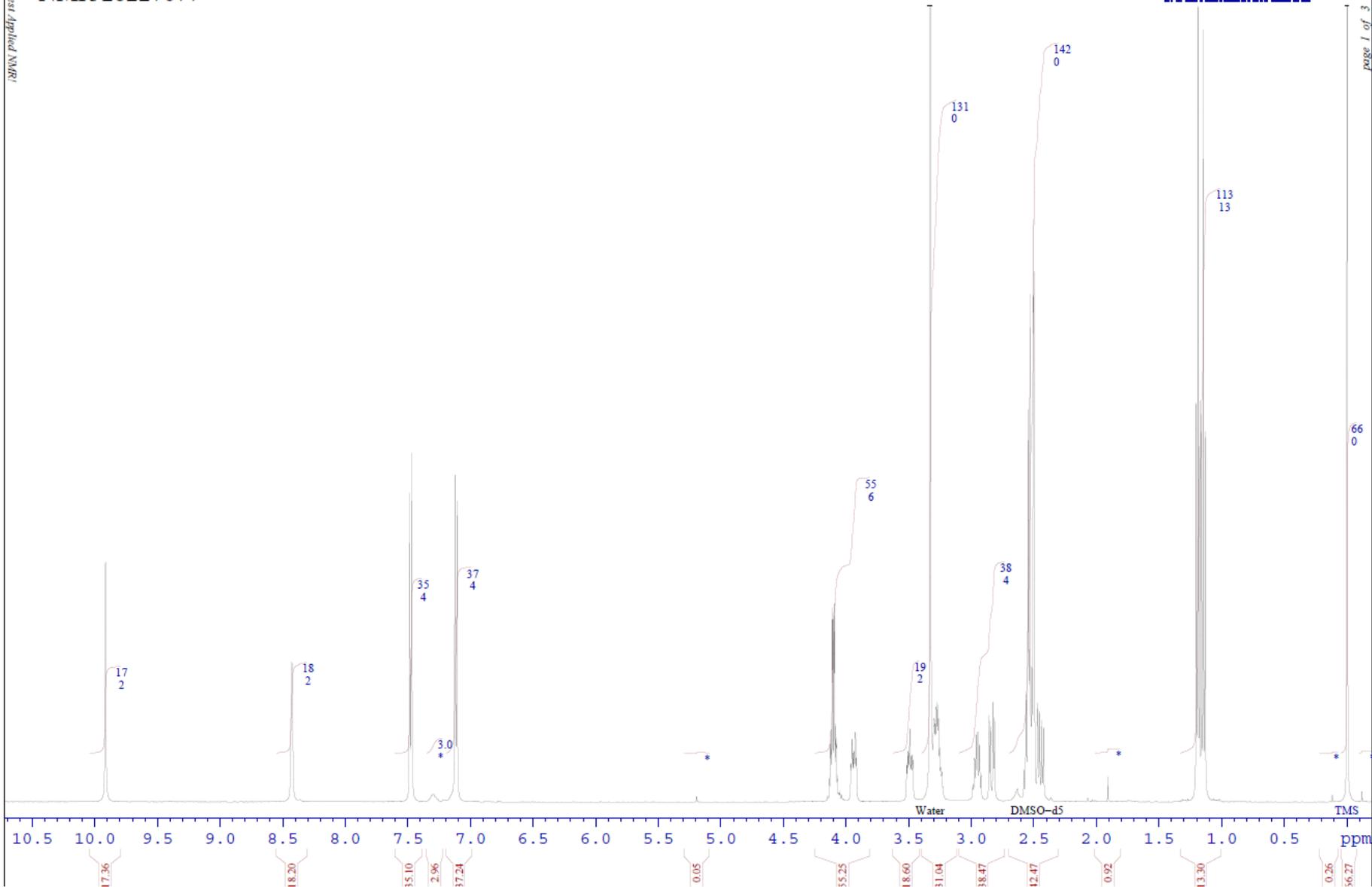
Yield: 1.60 g (80%), crystals of light beige color m.p. 236-237 °C.



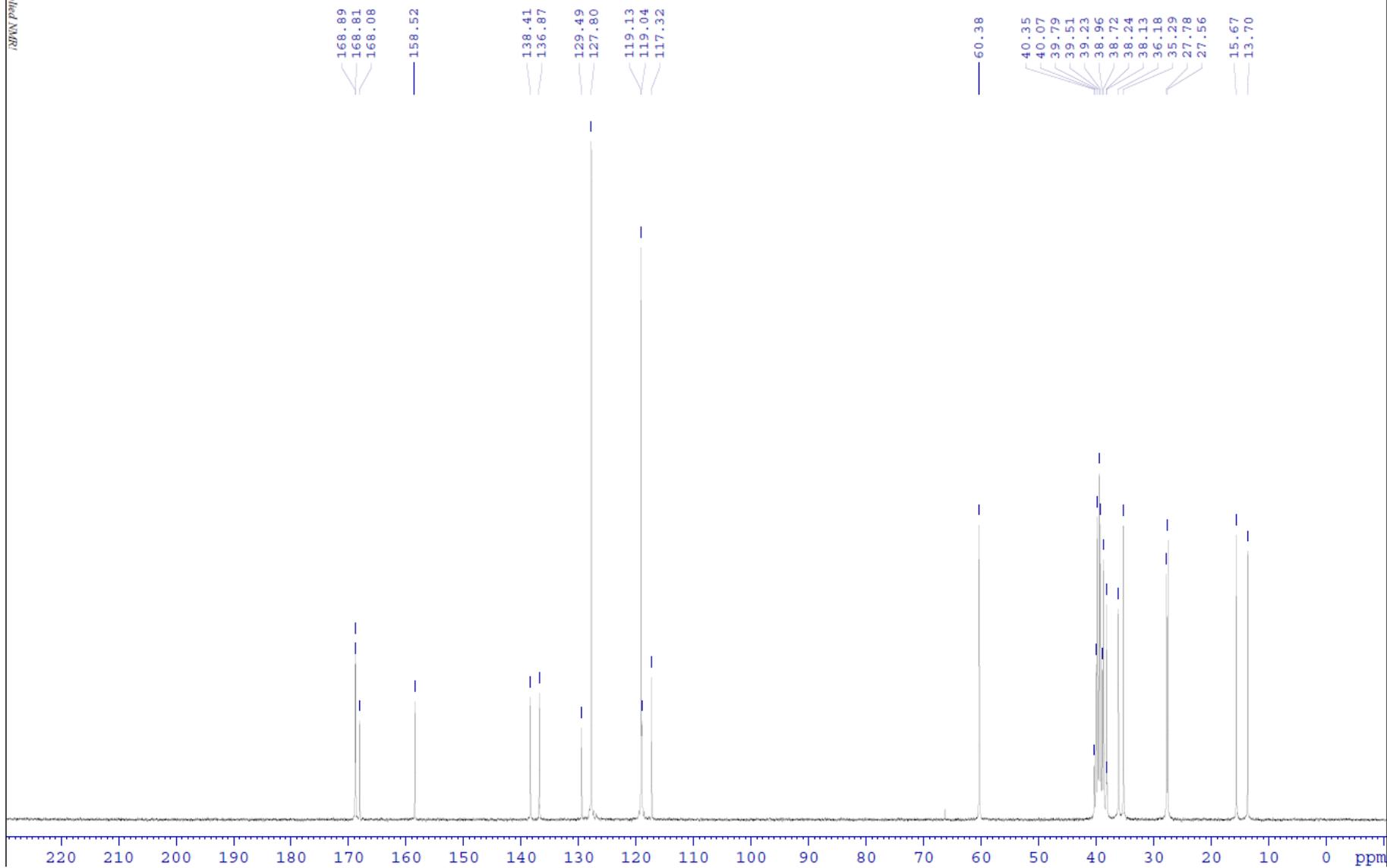
$^1\text{H}$  NMR, ( $\delta$ , ppm.,  $J/\text{Hz}$ ): 9.91 (1H, s, NH) 8.42(1H, s, NH); 7.48-7.10 (4H, m, Ar); 4.13-4.07 (4H, m, O-CH<sub>2</sub>+CH<sub>2</sub>); 3.96-3.91 (1H, m, CH<sup>8</sup>); 3.49-3.46 (1H, m, CH<sub>2</sub><sup>8</sup>); 3.29-3.26 (2H, m, CH<sub>2</sub><sup>3</sup>); 2.98-2.91 (1H, m, CH<sup>7</sup>); 2.84 (1H, dd,  $J_1 = 15.4$ ,  $J_2 = 5.5$ , CH<sub>2</sub>-CO); 2.56-2.51 (2H, m, CH<sub>2</sub><sup>4</sup>); 2.44 (1H, dd,  $J_1 = 15.6$ ,  $J_2 = 7.4$ , CH<sub>2</sub>-CO); 1.19 (3H, t,  $J = 7.14$ , CH<sub>3</sub>); 1.14 (3H, t,  $J = 7.6$ , CH<sub>3</sub>);  $^{13}\text{C}$  NMR ( $\delta$ , ppm): 168.89 (COOEt); 168.81 (C<sup>6</sup>); 168.08 (C<sup>1</sup>); 158.52 (CONH); 138.41 (C<sup>1'</sup>); 136.87 (C<sup>4'</sup>); 129.49 (C<sup>9a</sup>); 127.80 (C<sup>3'</sup>, C<sup>5'</sup>); 119.13 (C<sup>2'</sup>, C<sup>6'</sup>); 117.32 (C<sup>9</sup>); 60.38 (OCH<sub>2</sub>CH<sub>3</sub>); 38.72 (C<sup>8</sup>); 38.13 (C<sup>3</sup>); 36.18 (CH<sub>2</sub>-CO); 35.29 (C<sup>7</sup>); 27.78 (C<sup>4</sup>); 27.56 (CH<sub>2</sub>-CH<sub>3</sub> (Ar)); 15.67 (CH<sub>3</sub>); 13.70 (CH<sub>3</sub>); HRMS (ESI): Found,  $m/z$  400.1867 [M+H]<sup>+</sup>. C<sub>21</sub>H<sub>25</sub>N<sub>3</sub>O<sub>5</sub> Calculated, [M+H] 400.1868.

NMR/28227677

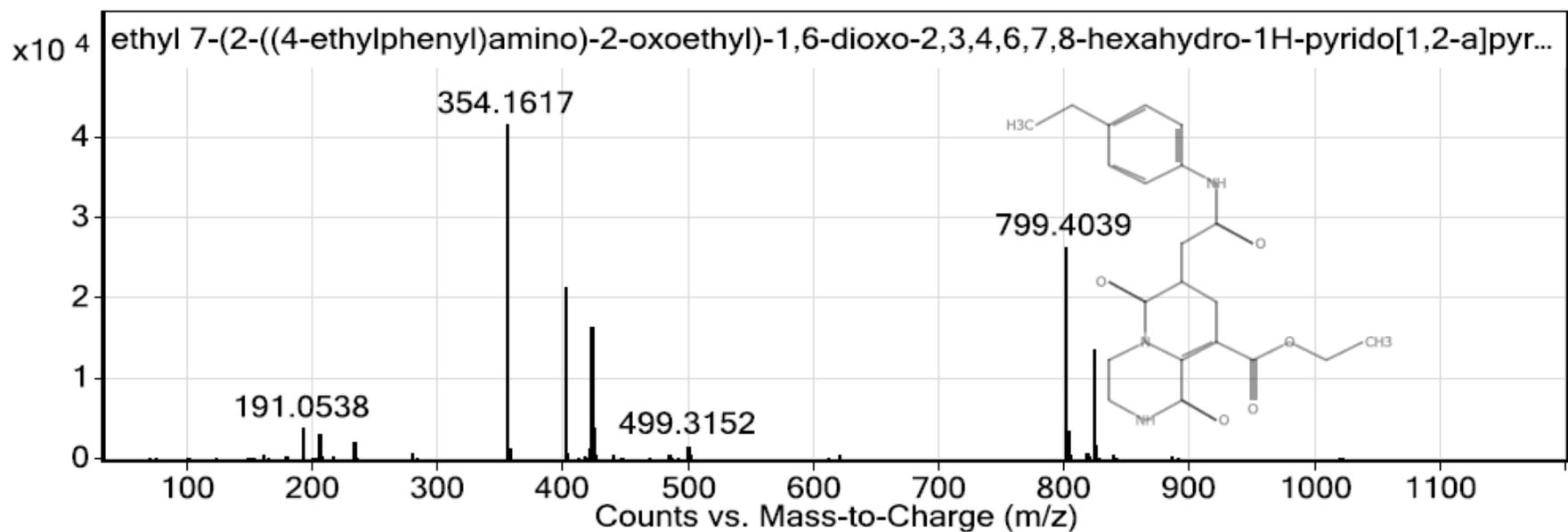
Found protons = 37 impurity\* = 1.2 %



/PREZ Ja-79







MS Spectrum Peak List

<i>m/z</i>	<i>z</i>	Abund
191.0538		3913.28
354.1617	1	41688.78
355.1648	1	8908.61
400.1867	1	21537.31
401.2096	1	5207.34
422.1885	1	16372.3
799.4039	1	26505.81
800.4073	1	12786.21
821.3872	1	13824.64
822.3915	1	6651.08