Supporting Information

Practical Synthesis of MDM2 Antagonist RG7388. Part 1: A Cu(II)-Catalyzed Asymmetric [3+2] Cycloaddition

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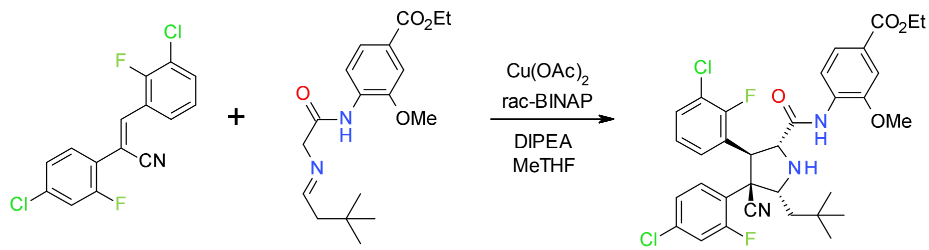
Detailed procedure for the preparation of *rac*-**15**, *rac*-**16**

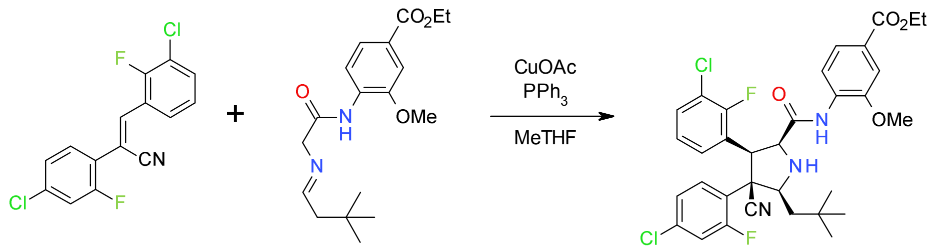
***rac*-Ethyl 4-[[(2R,3S,4R,5R)-4-(2-chloro-4-fluorophenyl)-3-(3-chloro-2-fluorophenyl)-4-cyano-5-(2,2-dimethylpropyl)pyrrolidine-2-carbonyl]amino]-3-methoxybenzoate (*rac*-15)**



3 **8** *rac*-**15**

A mixture of $Cu(OAc)_2$ (7.5 mg, 41.3 μmol) and *rac*-BINAP (28.0 mg, 45.0 μmol) was suspended in MeTHF (6 mL) and stirred under N_2 at room temperature for 3 h. Then DIPEA (0.60 mL, 3.44 mmol) was added, followed by **3** (1.00 g, 3.22 mmol) and **8** (1.20 g, 3.59 mmol). The mixture was stirred at room temperature under N_2 overnight. The resulting suspension was diluted with EtOH (9.47 g, 12 mL), stirred at room temperature for 3 h, then filtered. The solid cake was washed with EtOH (15.8 g, 20 mL) and *n*-heptane (13.7 g, 20 mL), dried by suction to give *rac*-**15** (1.41 g, 67.8 % yield) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.66 (brs, 1H), 8.42 (d, *J* = 8.3 Hz, 1H), 7.89 (m, 1H), 7.65 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.55 (d, *J* = 1.8 Hz, 1H), 7.40 (m, 1H), 7.32 (td, *J* = 8.3, 1.5 Hz, 1H), 7.22-7.15 (m, 3H), 4.45 (m, 2H), 4.36 (q, *J* = 7.2 Hz, 2H), 4.25 (m, 1H), 3.91 (s, 3H), 1.39 (t, *J* = 7.2 Hz, 3H), 1.30 (dd, *J* = 14.2, 9.3 Hz, 1H), 0.92 (s, 9H), 0.84 (d, *J* = 14.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.72, 166.19, 161.17, 158.66, 157.73, 155.27, 147.68, 136.28, 136.17, 130.90, 130.61, 129.31, 127.00, 125.85, 125.45, 125.42, 125.21, 125.17, 125.12, 125.09, 123.16, 121.90, 121.70, 120.89, 120.77, 118.62, 117.53, 117.27, 110.68, 66.61, 65.69, 60.99, 57.28, 55.62, 45.74, 44.02, 30.55, 29.34, 14.34.

***rac*-Ethyl 4-[[(2S,3S,4R,5S)-4-(2-chloro-4-fluorophenyl)-3-(3-chloro-2-fluorophenyl)-4-cyano-5-(2,2-dimethylpropyl)pyrrolidine-2-carbonyl]amino]-3-methoxybenzoate (*rac*-16)**

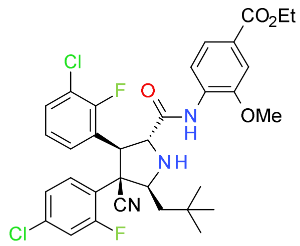


3 **8** ***rac*-16**

A suspension of CuOAc (5.0 mg, 40.8 μmol) and triphenylphosphine (22.0 mg, 83.9 μmol) in MeTHF (8 mL) was stirred at room temperature under N_2 for 3 h. Compound **3** (1.00 g, 3.22 mmol) and **8** (1.20 g, 3.59 mmol) were added and the mixture was stirred at room temperature under N_2 overnight. The resulting solution was washed with 5% aq. NH_4OAc (2 × 5.0 mL), 5% of aq. NaCl (5.0 mL), and concentrated to give a foam. This foam was re-dissolved in EtOH (20 mL) and stirred at room temperature over weekend. The slurry was filtered and washed with EtOH (10 mL) to give a 1:5 mixture of *rac*-**15** and *rac*-**16** (1.75 g, 84.2% yield). Analytical sample of pure *rac*-**16** was obtained by column chromatography on silica gel. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.97 (brs, 1H), 8.30 (d, *J* = 8.4 Hz, 1H), 7.65 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.56 (d, *J* = 1.7 Hz, 1H), 7.51 (m, 1H), 7.43 (t, *J* = 8.4 Hz, 1H), 7.23 (m, 1H), 7.17 (dd, *J* =12.6, 2.0 Hz, 1H), 7.11 (m, 1H), 6.89 (td, *J* = 8.1, 1.2 Hz, 1H), 5.05 (dd, *J* = 10.8, 2.1 Hz, 1H), 4.53 (d, *J* = 10.8 Hz, 1H), 4.37 (q, *J* = 7.2 Hz, 2H), 4.22 (d, *J* = 8.7 Hz, 1H), 3.95 (s, 3H), 1.85 (dd, *J* = 14.1, 8.7 Hz, 1H), 1.48 (d, *J* =14.1 Hz, 1H), 1.40 (t, *J* = 7.2 Hz, 1H), 0.97 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.08, 166.24, 160.84, 158.34, 157.87, 155.40, 148.08, 136.51, 136.40, 131.75, 131.71, 130.85, 130.43, 127.94, 125.94, 125.45, 125.42, 124.17, 124.12, 123.14, 120.98, 120.79, 118.41, 118.13, 117.86, 110.95, 62.34, 60.95, 60.72, 58.24, 56.17, 45.73, 44.96, 30.28, 29.84, 14.35.

NMR data of **10**, **33**, 3**4**

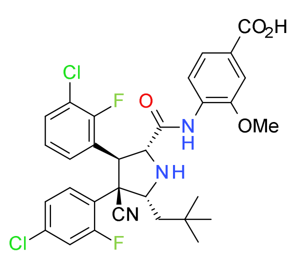
***rac*-Ethyl 4-[[(2R,3S,4R,5S)-3-(3-chloro-2-fluoro-phenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-(2,2-dimethylpropyl)pyrrolidine-2-carbonyl]amino]-3-methoxybenzoate (*rac*-10)**



rac-**10**

Rac-**10** was obtained from the esterification of *rac*-**1**. ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.41 (s, 1H), 8.47 (d, *J* = 8.4 Hz, 1H), 7.68 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.59 (d, *J* = 1.8 Hz, 1H), 7.49 (m, 1H), 7.32 (m, 1H), 7.25 (t, *J* = 8.4 Hz, 1H), 7.17 (dd, *J* = 12.3, 2.1 Hz, 1H), 7.15 (t, *J* = 7.9 Hz, 1H), 7.11 (dd, *J* = 8.5, 2.2 Hz, 1H), 4.77 (d, *J* = 8.5 Hz, 1H), 4.55 (t, *J* = 9.2 Hz, 1H), 4.37 (m, 2H), 4.10 (m, 1H), 3.95 (s, 3H), 2.79 (t, *J* = 11.0 Hz, 1H), 1.59 (dd, *J* =14.5, 9.8 Hz, 1H), 1.40 (t, *J* = 7.2 Hz, 3H), 1.40 (m, 1H), 1.02 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.39, 166.31, 160.62, 158.95, 157.46, 155.81, 147.89, 136.39, 136.32, 131.35, 131.32, 131.19, 130.46, 127.38, 125.82, 125.36, 125.34, 124.76, 124.69, 124.66, 123.31, 121.62, 121.50, 118.25, 117.96, 117.88, 117.81, 117.78, 117.76, 110.73, 65.14, 65.10, 64.34, 63.17, 63.11, 61.04, 55.69, 50.34, 50.31, 45.03, 30.48, 29.82, 14.41.

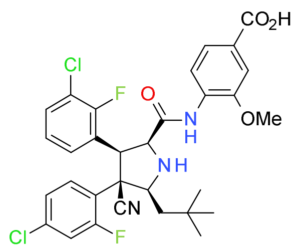
***rac*-4-[[(2R,3S,4R,5R)-3-(3-chloro-2-fluoro-phenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-(2,2-dimethylpropyl)pyrrolidine-2-carbonyl]amino]-3-methoxybenzoic acid (*rac*-33)**



rac-**33**

Rac-**13** was hydrolyzed with aq. NaOH to give a mixture of *rac*-**33** and *rac*-**1**. Pure *rac*-**33** was obtained by preparative SFC. ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.85 (br, 1H), 9.96 (s, 1H), 8.25 (d, *J* = 8.5 Hz, 1H), 7.93 (m, 1H), 7.65 (dd, *J* = 11.6, 1.9 Hz, 1H), 7.59 (m, 1H), 7.56-7.52 (m, 2H), 7.41-7.31 (m, 3H), 4.55-4.45 (m, 2H), 4.34 (d, J = 8.9 Hz, 1H), 4.15 (m, 1H), 3.90 (s, 3H), 1.29 (dd, J = 13.7, 9.3 Hz, 1H), 0.88 (s, 9H), 0.80 (d, J =13.7 Hz, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 170.87, 167.33, 160.90, 159.23, 157.13, 155.49, 148.27, 135.43, 135.36, 131.14, 130.82, 129.97, 128.51, 126.59, 126.19, 126.11, 126.06, 126.03, 125.99, 123.07, 122.07, 121.99, 120.85, 120.63, 120.50, 118.73, 118.03, 117.85, 111.60, 66.13, 65.09, 56.30, 46.70, 44.77, 30.92, 30.75, 29.75.

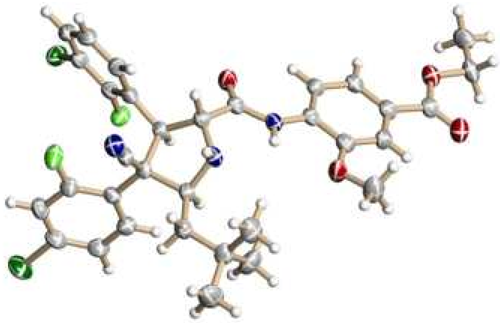
***rac*-4-[[(2S,3S,4R,5S)-3-(3-Chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-(2,2-dimethylpropyl)pyrrolidine-2-carbonyl]amino]-3-methoxybenzoic acid (*rac*-34)**

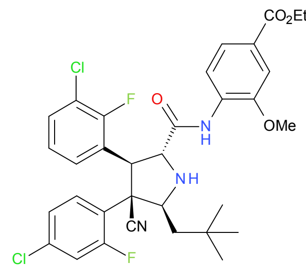


rac-**34**

Rac-**34** was obtained from enzymatic hydrolysis of *rac*-**14** and was purified by preparative HPLC. ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.83 (brs, 1H), 10.50 (s, 1H), 8.11 (d, J = 8.3 Hz, 1H), 7.60 (dd, J = 12.6, 2.2 Hz, 1H), 7.53 (dd, J = 8.3, 1.7 Hz, 1H), 7.52-7.47 (m, 2H), 7.45-7.38 (m, 2H), 7.37 (dd, J = 8.6, 2.1 Hz, 1H), 7.05 (td, J = 8.1, 0.6 Hz, 1H), 4.86 (d, J = 10.4 Hz, 1H), 4.47 (d, J = 10.4 Hz, 1H), 4.17 (br, 1H), 4.08 (d, J = 9.2 Hz, 1H), 3.89 (s, 3H), 1.71 (dd, J = 13.6, 9.4 Hz, 1H), 1.38 (d, J = 13.6 Hz, 1H), 0.93 (s, 9H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 169.50, 167.39, 160.82, 159.15, 157.34, 155.70, 148.64, 135.38, 135.31, 131.72, 131.69, 131.31, 130.30, 128.43, 126.49, 126.24, 126.22, 124.98, 124.95, 124.35, 124.26, 123.09, 119.79, 119.73, 119.67, 118.69, 118.63, 118.39, 118.21, 117.76, 62.21, 61.58, 61.55, 57.35, 57.31, 56.65, 46.82, 46.02, 30.53, 30.21.

X-ray crystallographic result for **10**, **15** and **16**





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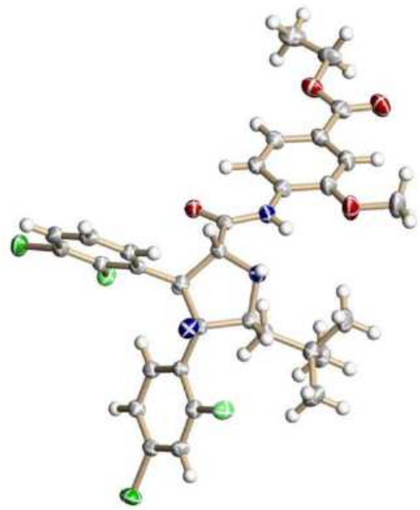

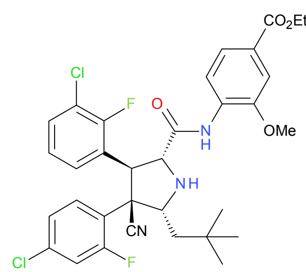

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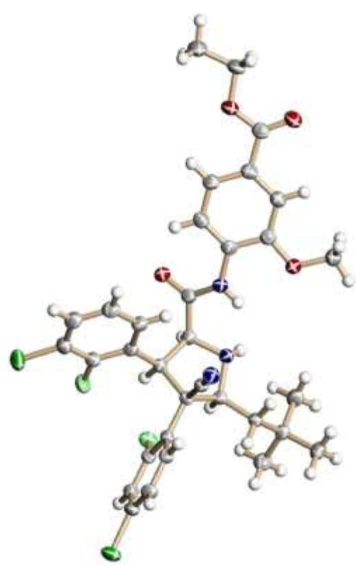

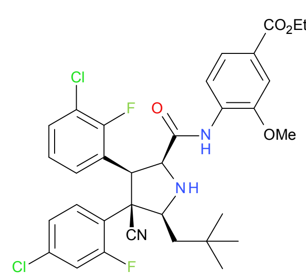

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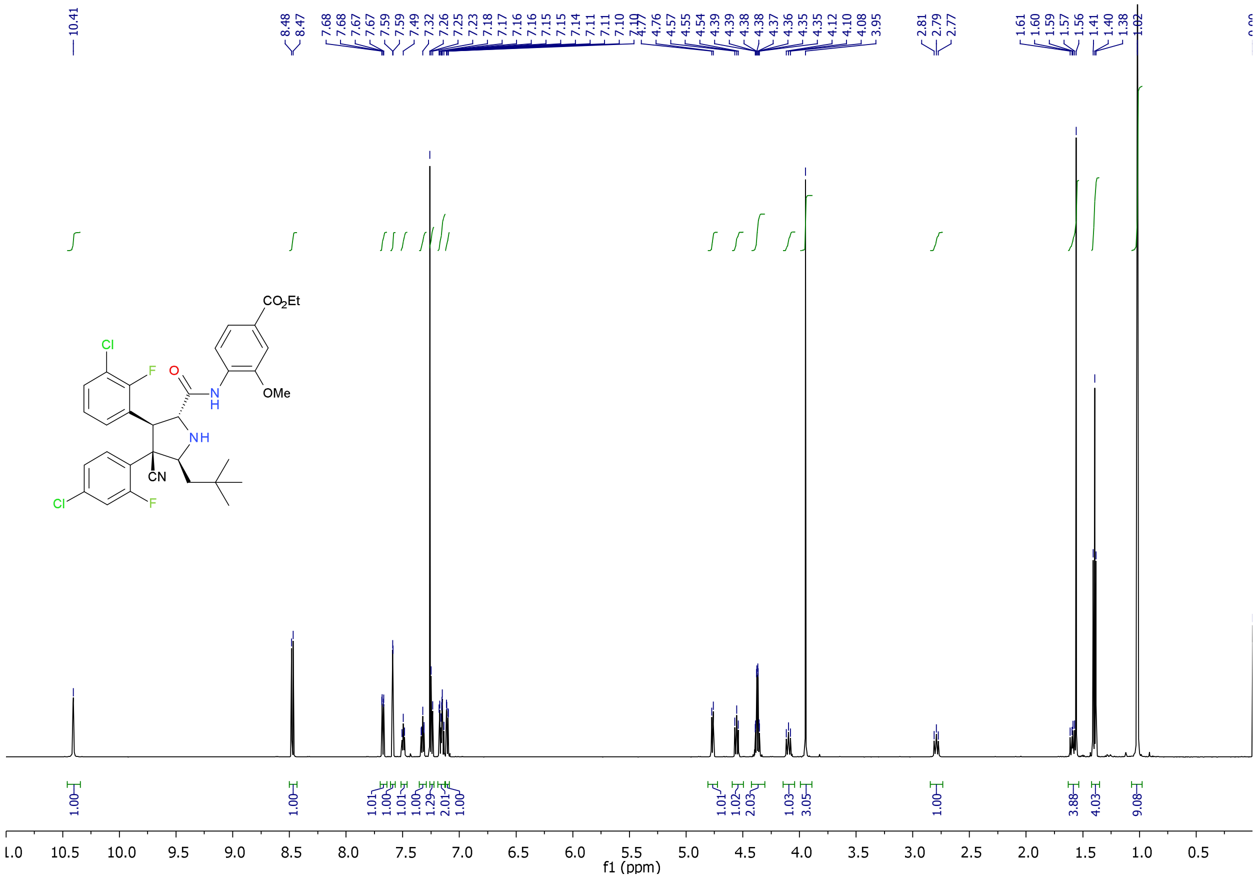
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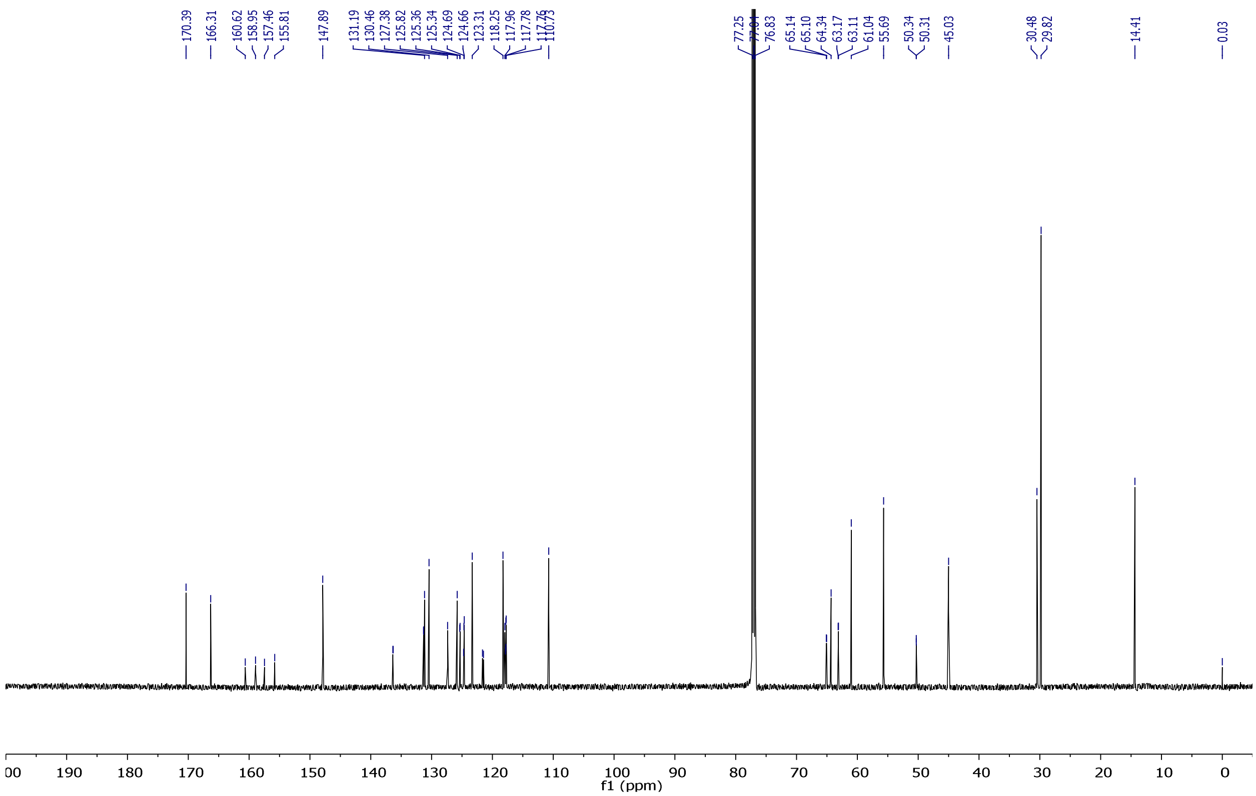
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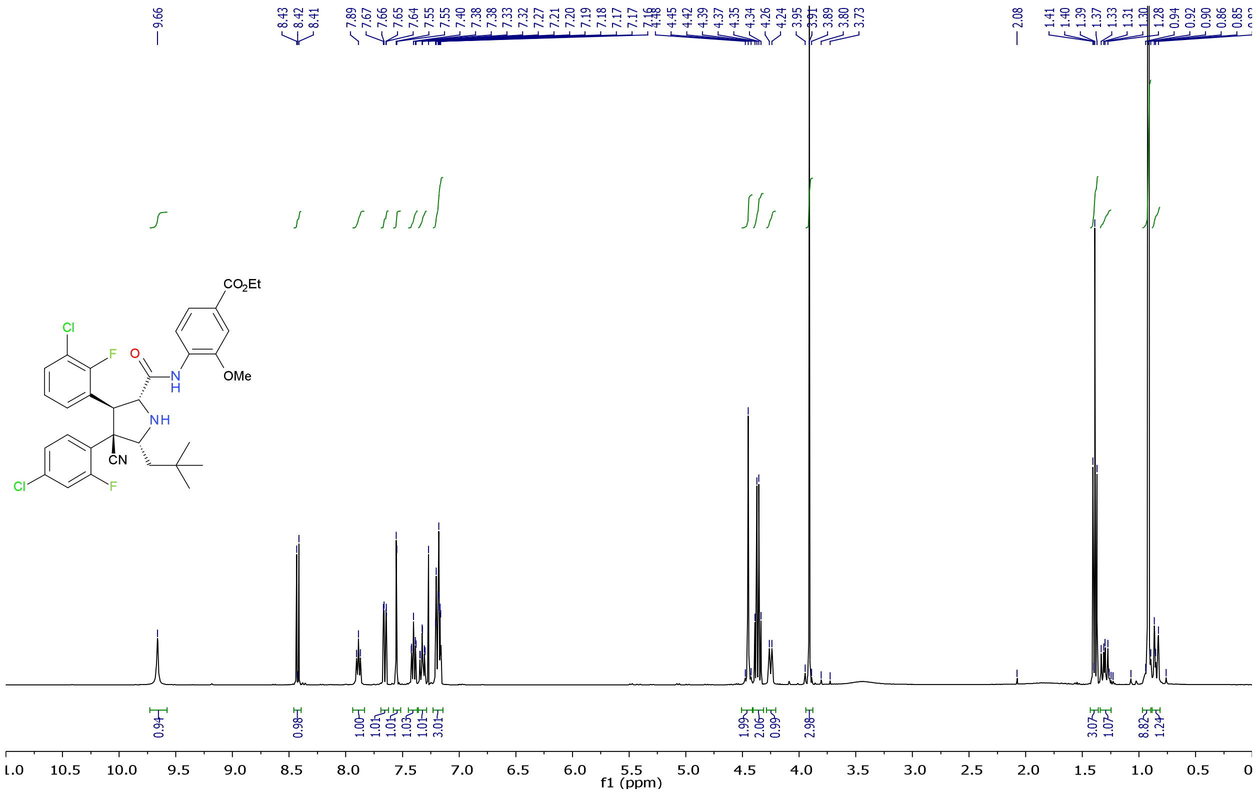

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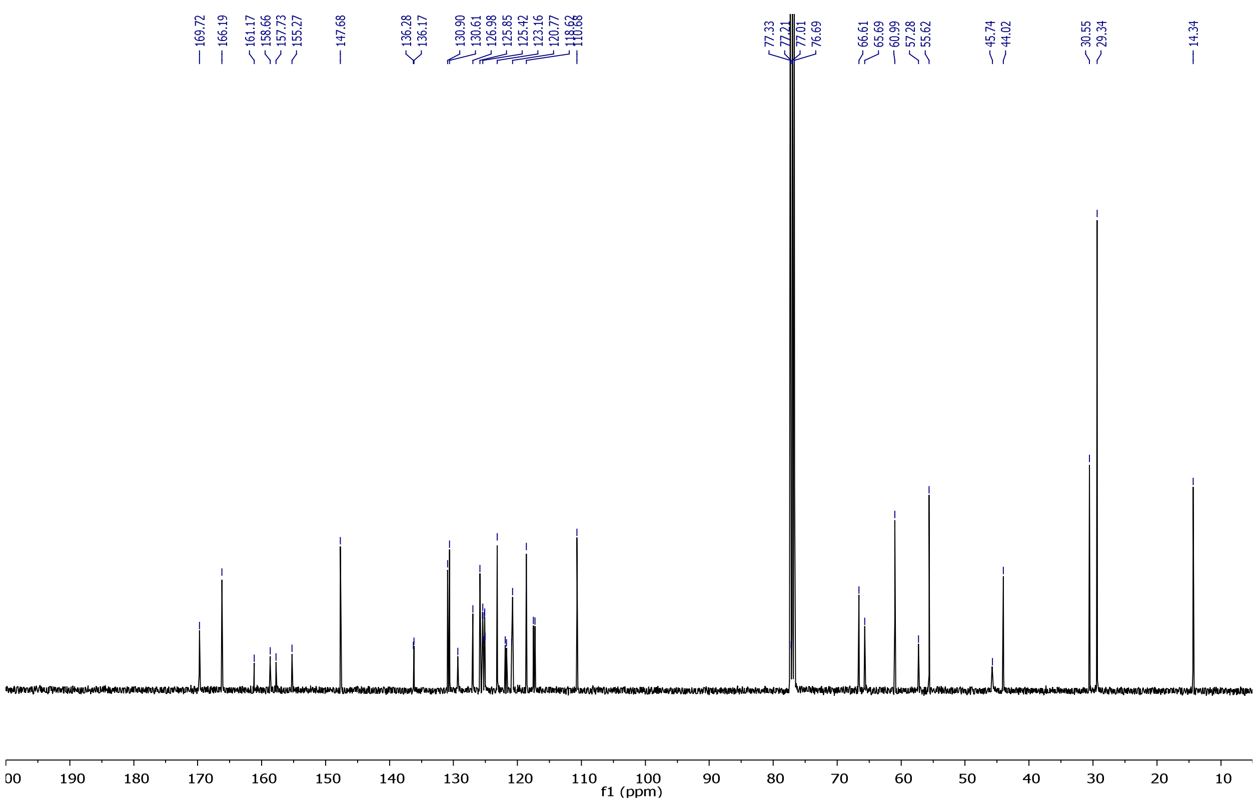

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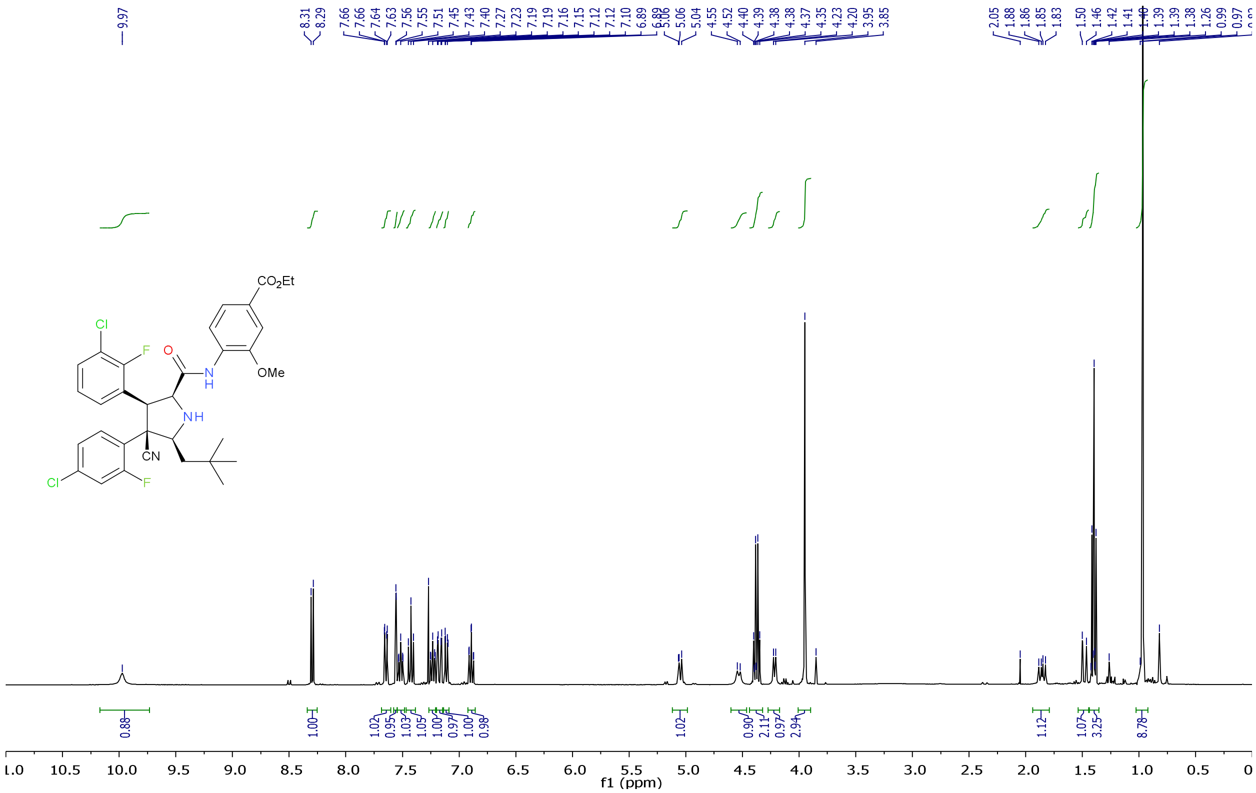
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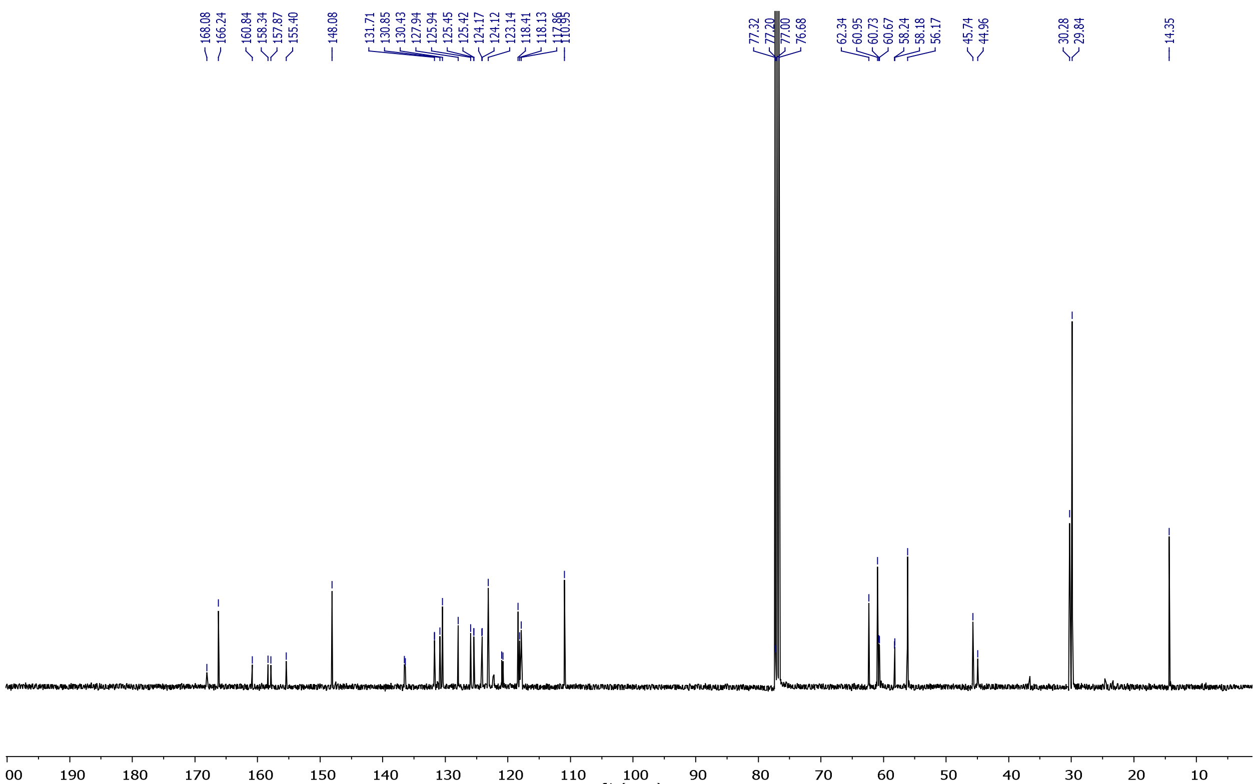
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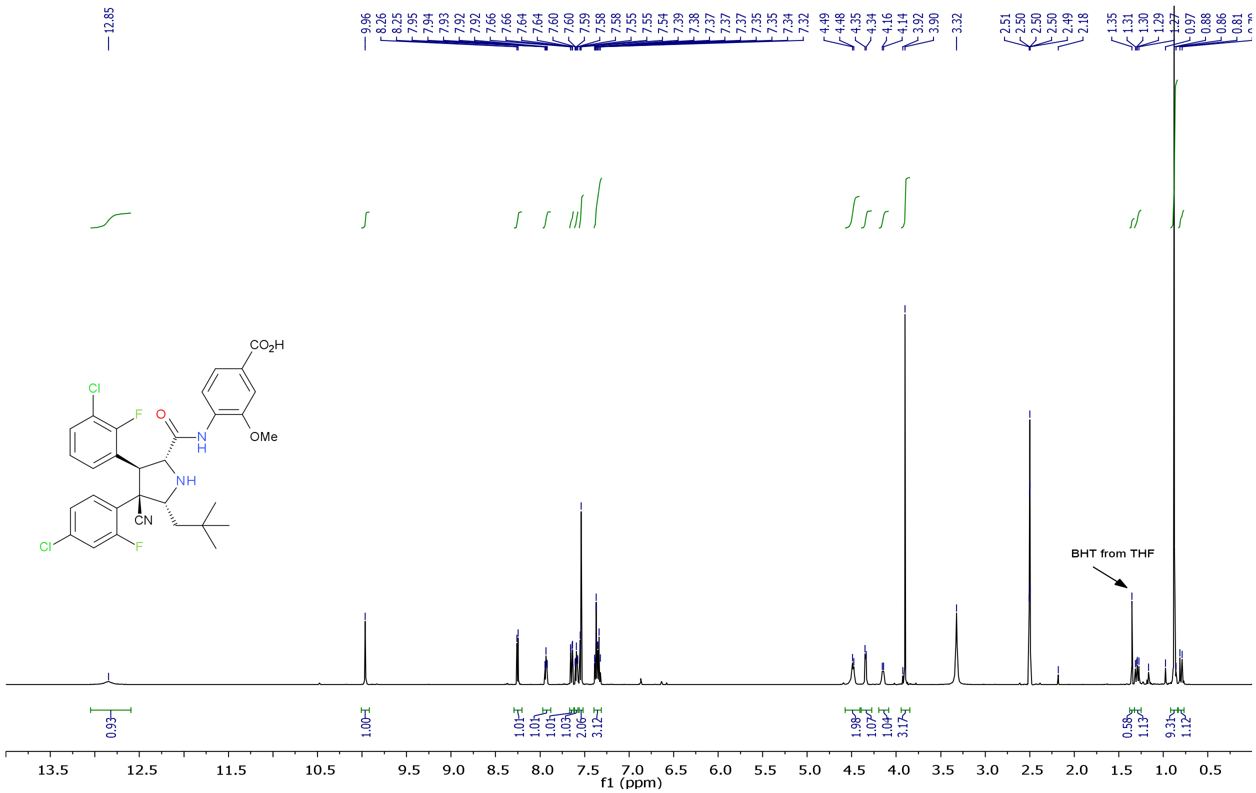
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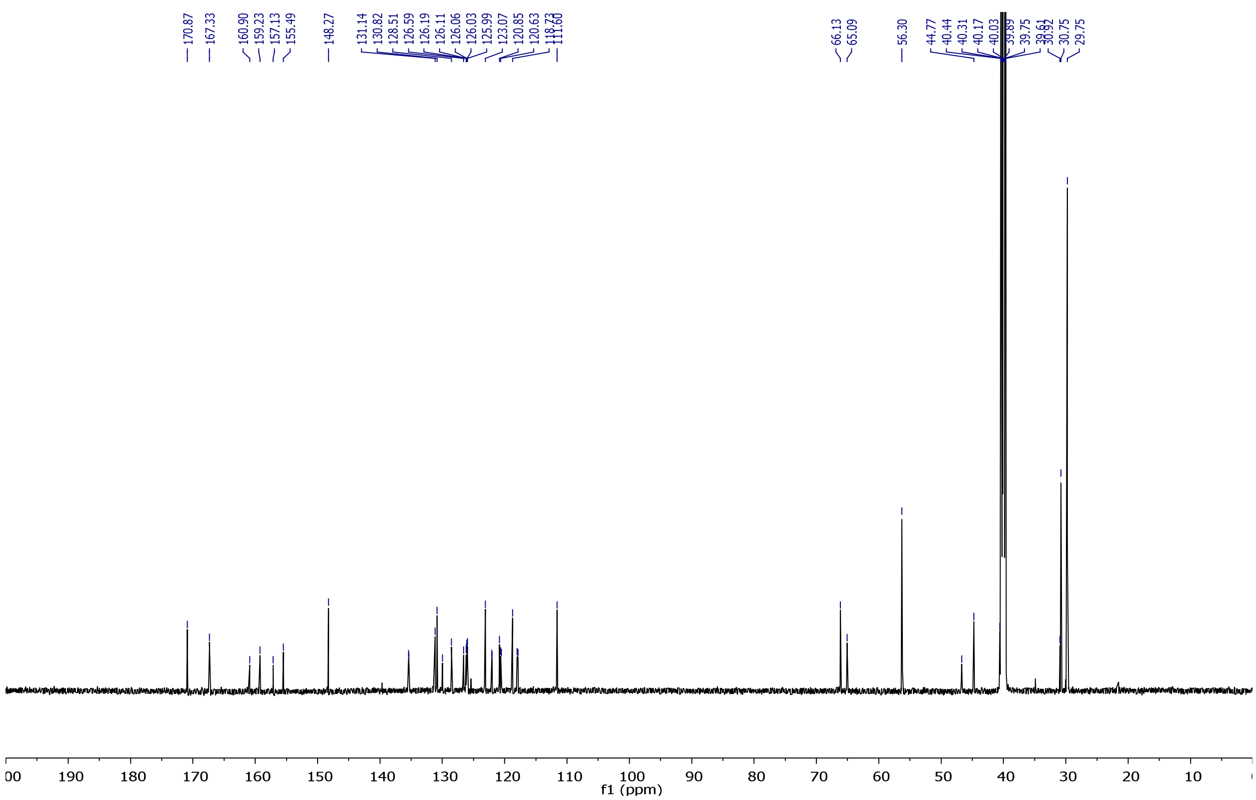
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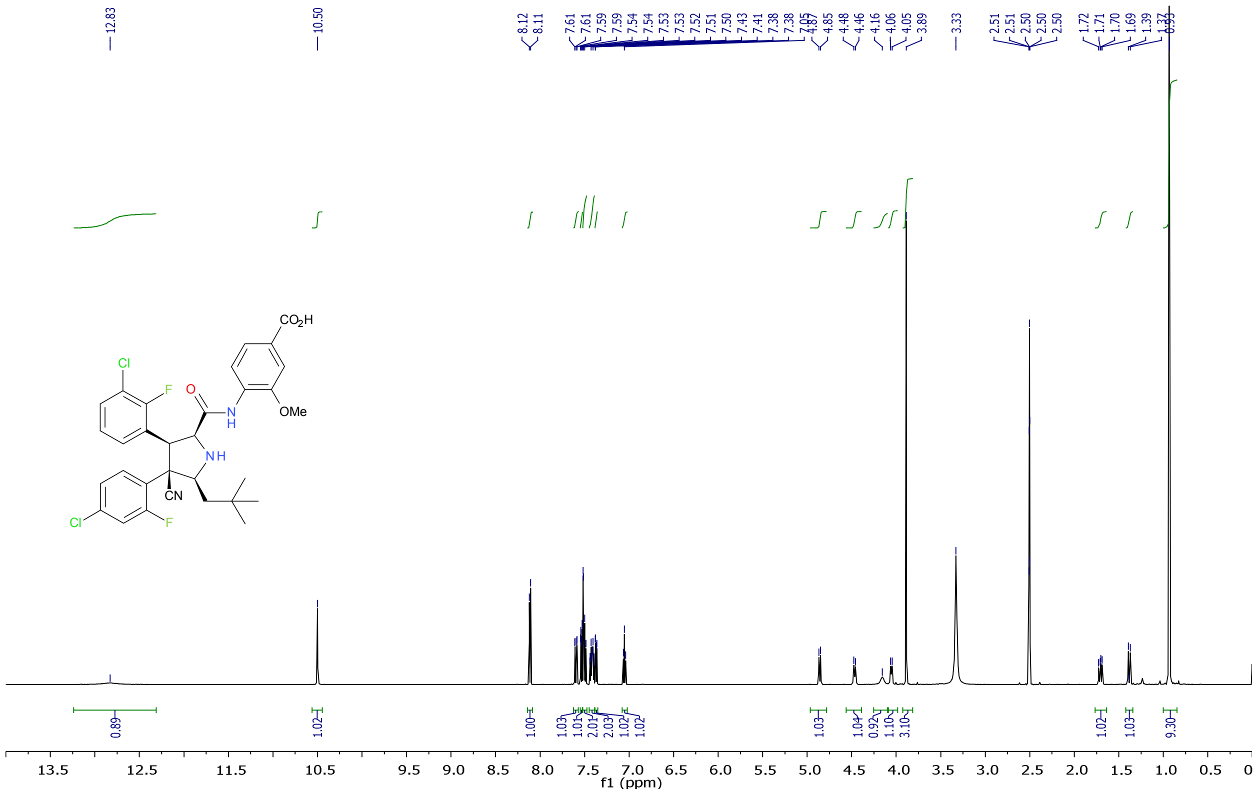
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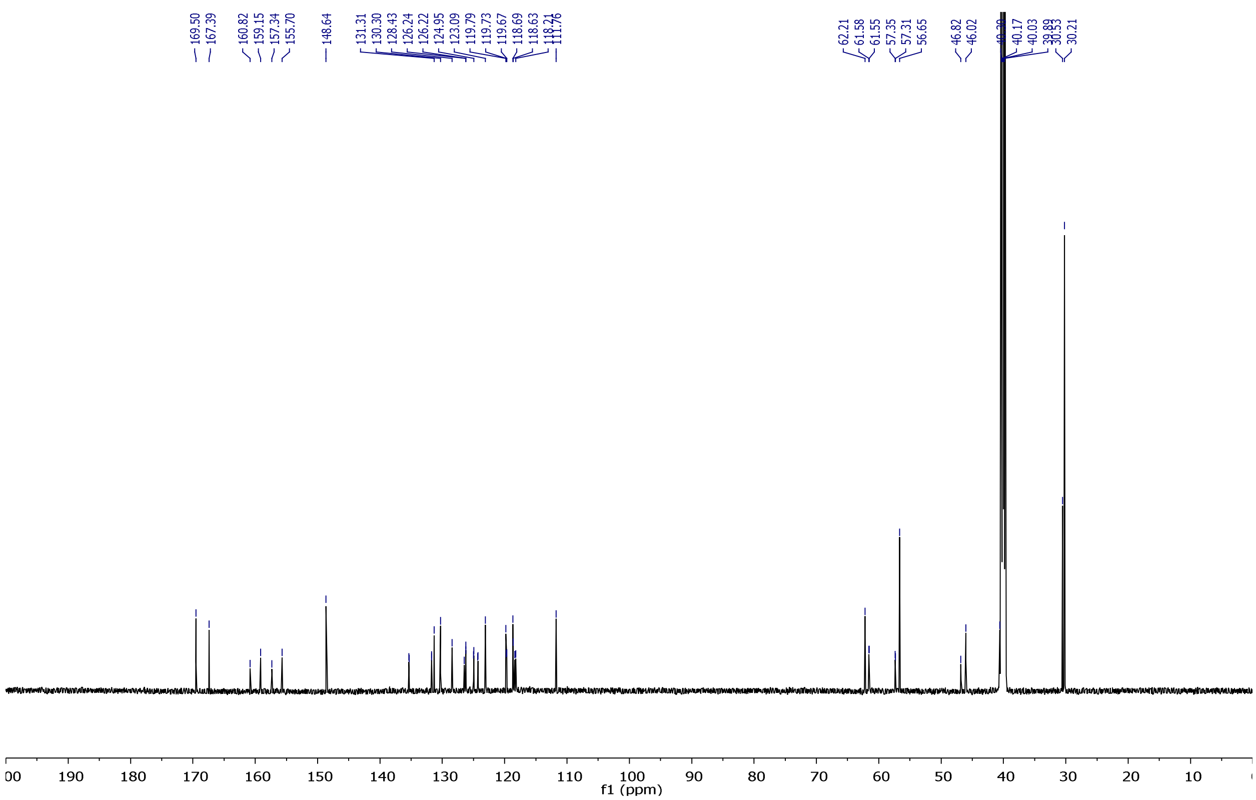
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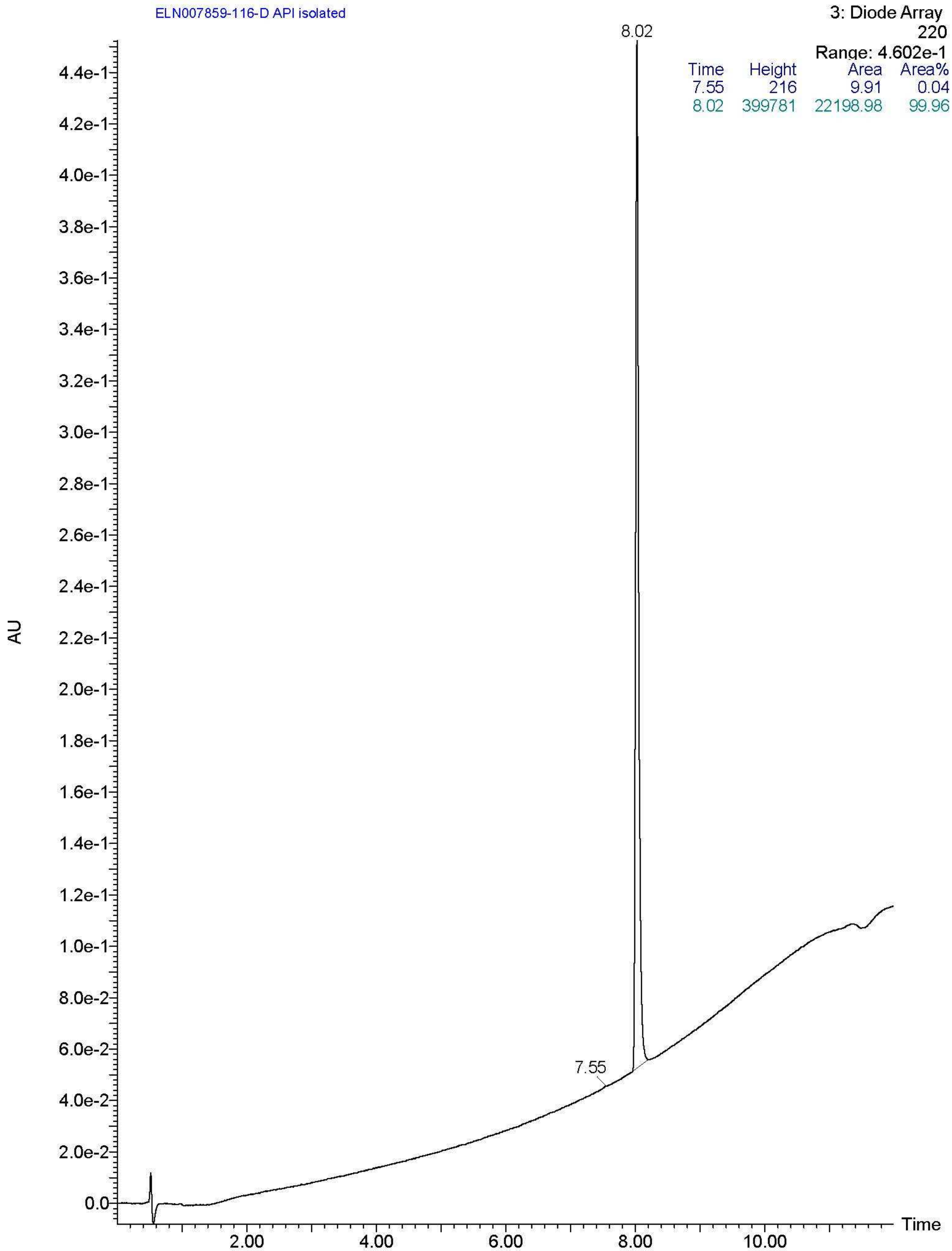
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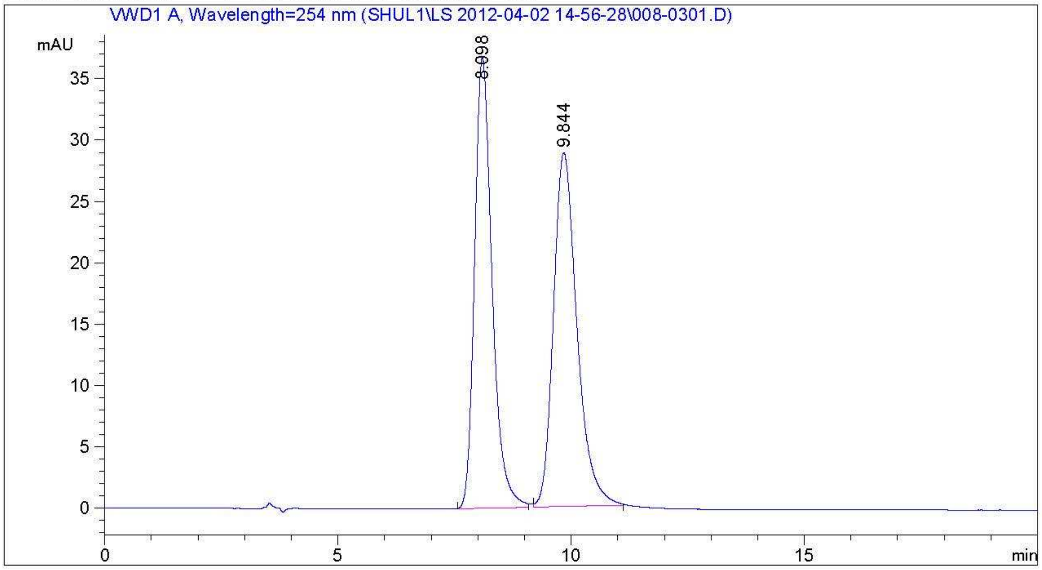

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Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	8.098	BB	0.3954	956.88763	36.76637	48.6806
2	9.844	BB	0.5333	1008.75812	28.83627	51.3194

Totals : 1965.64575 65.60264

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*** End of Report ***

Data File C:\CHEM32\1\DATA\SHUL1\LS 2012-04-03 10-13-38\010-0101.D
Sample Name: 7859-116-D

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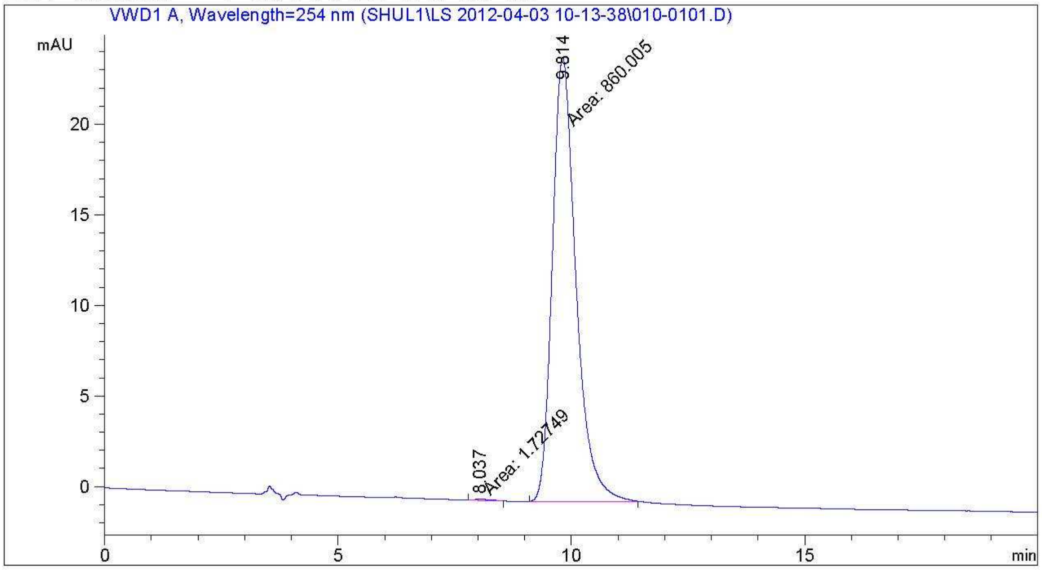
```
Acq. Operator   :                                    Seq. Line :    1
Acq. Instrument : LC                                  Location : Vial 10
Injection Date  : 4/3/2012 10:24:35 AM                     Inj :    1
                                                    Inj Volume : 1 µl
Acq. Method     : C:\Chem32\1\DATA\SHUL1\LS 2012-04-03 10-13-38\MDM2(4).M
Last changed    : 11/16/2011 4:39:33 PM
Analysis Method : C:\CHEM32\1\DATA\SHUL1\LS 2012-04-03 10-13-38\010-0101.D\DA.M (MDM2(4).M)
Last changed    : 11/16/2011 4:39:33 PM
```



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Area Percent Report

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Sorted By	:	Signal
Multiplier	:	1.0000
Dilution	:	1.0000

Use Multiplier & Dilution Factor with ISTDs

Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	8.037	MM	0.4254	1.72749	6.76850e-2	0.2005
2	9.814	MM	0.5847	860.00543	24.51359	99.7995
Totals :				861.73292	24.58128	

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*** End of Report ***