Supplementary Information

The First Optimization of Novel, Potent, Selective PDE11A4 Inhibitors for Age-Related Cognitive Decline

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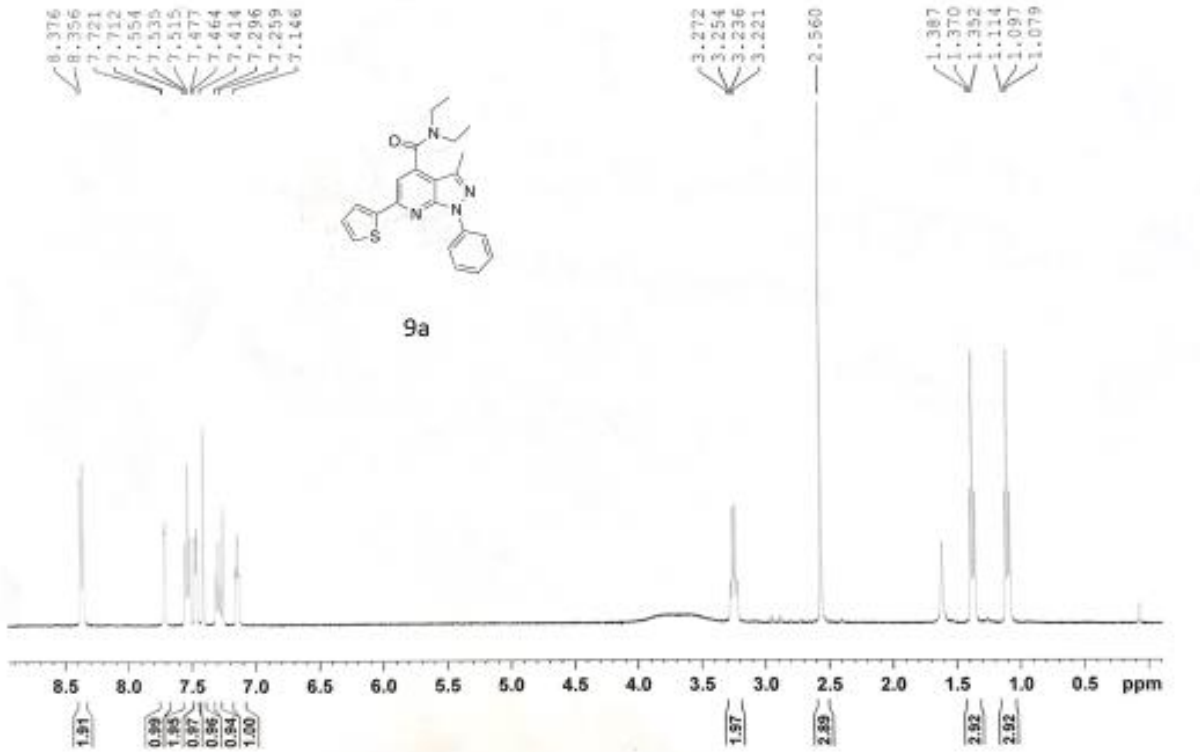
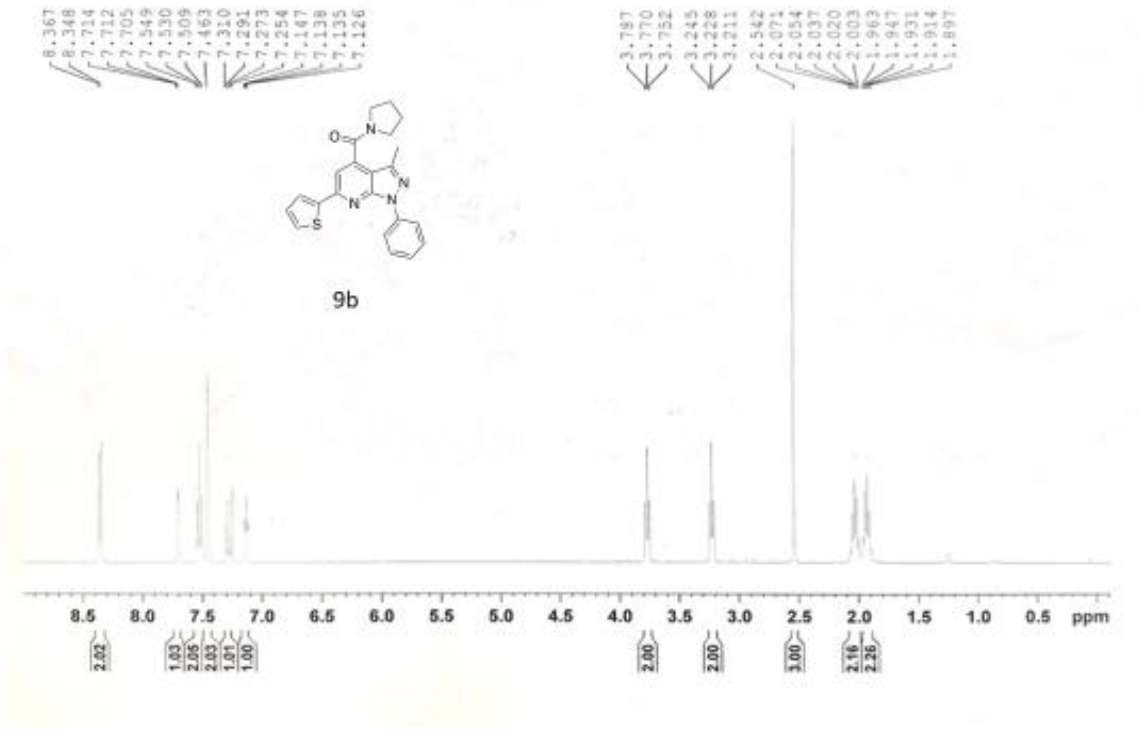
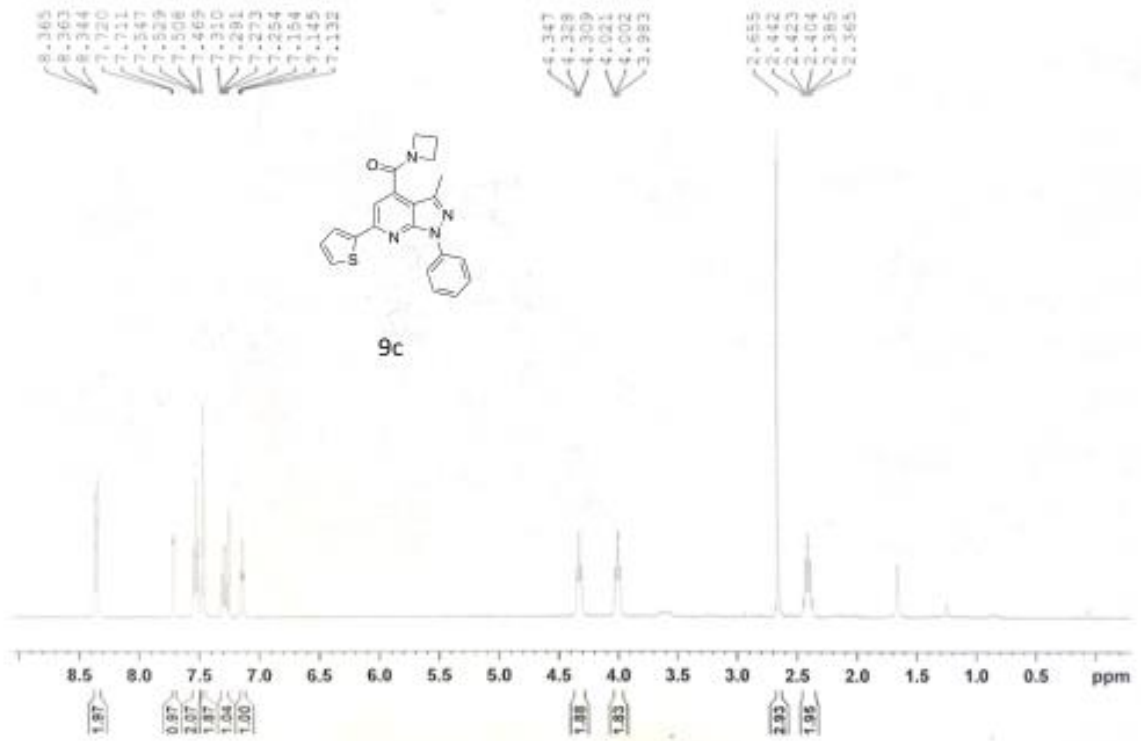
Proton NMR and HPLC data of Final Compounds



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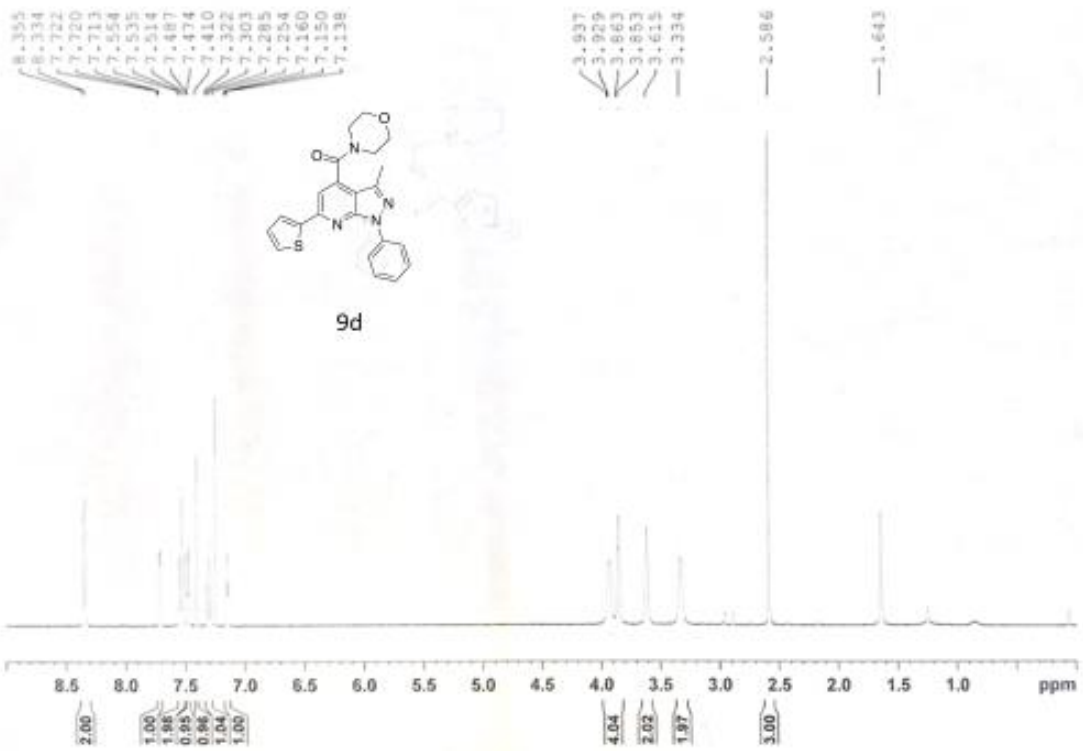
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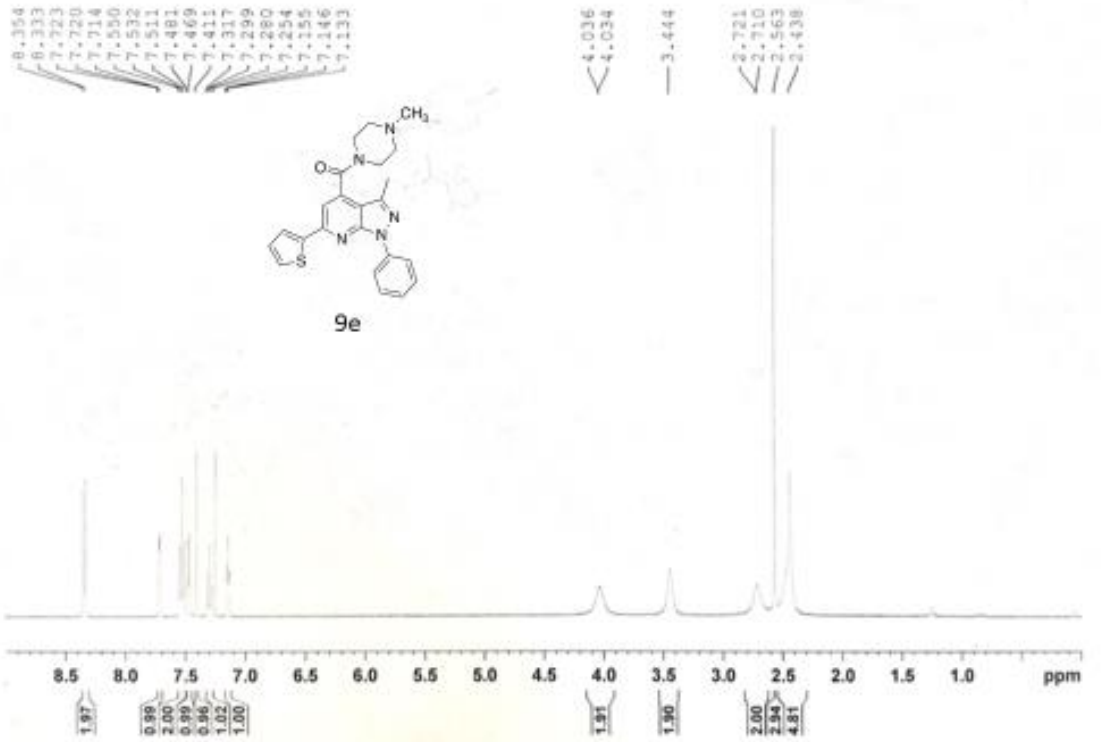
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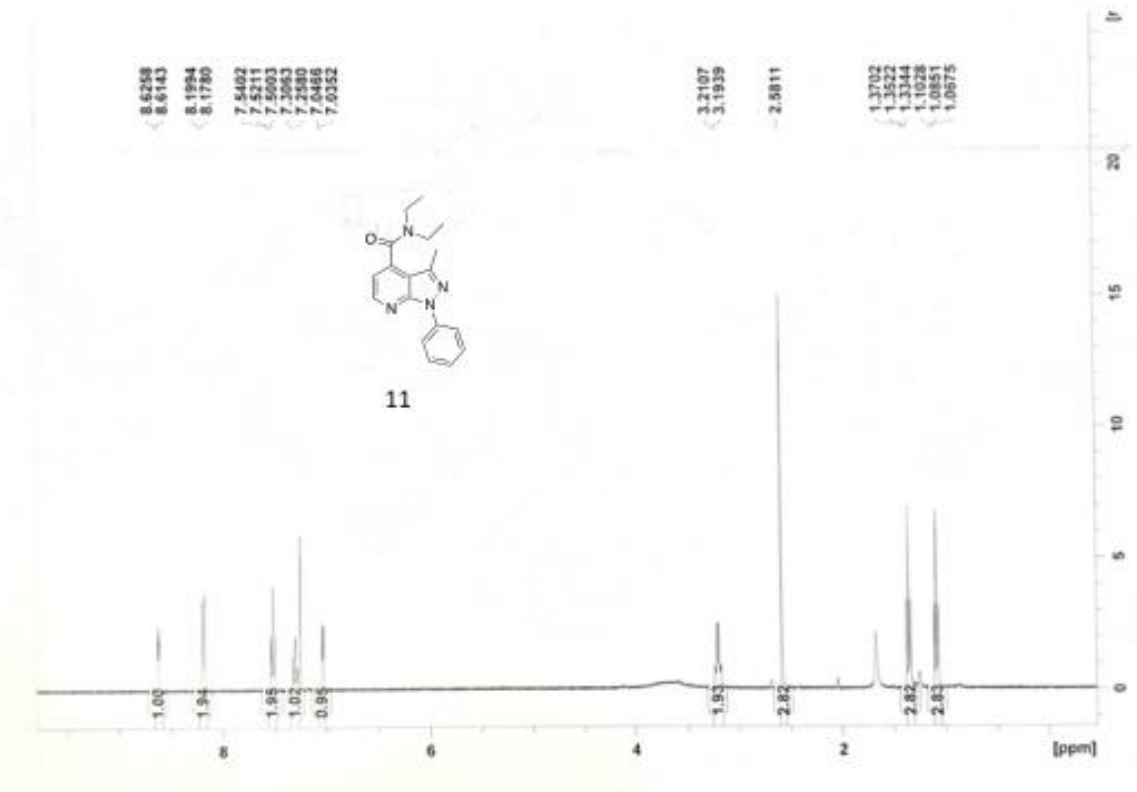
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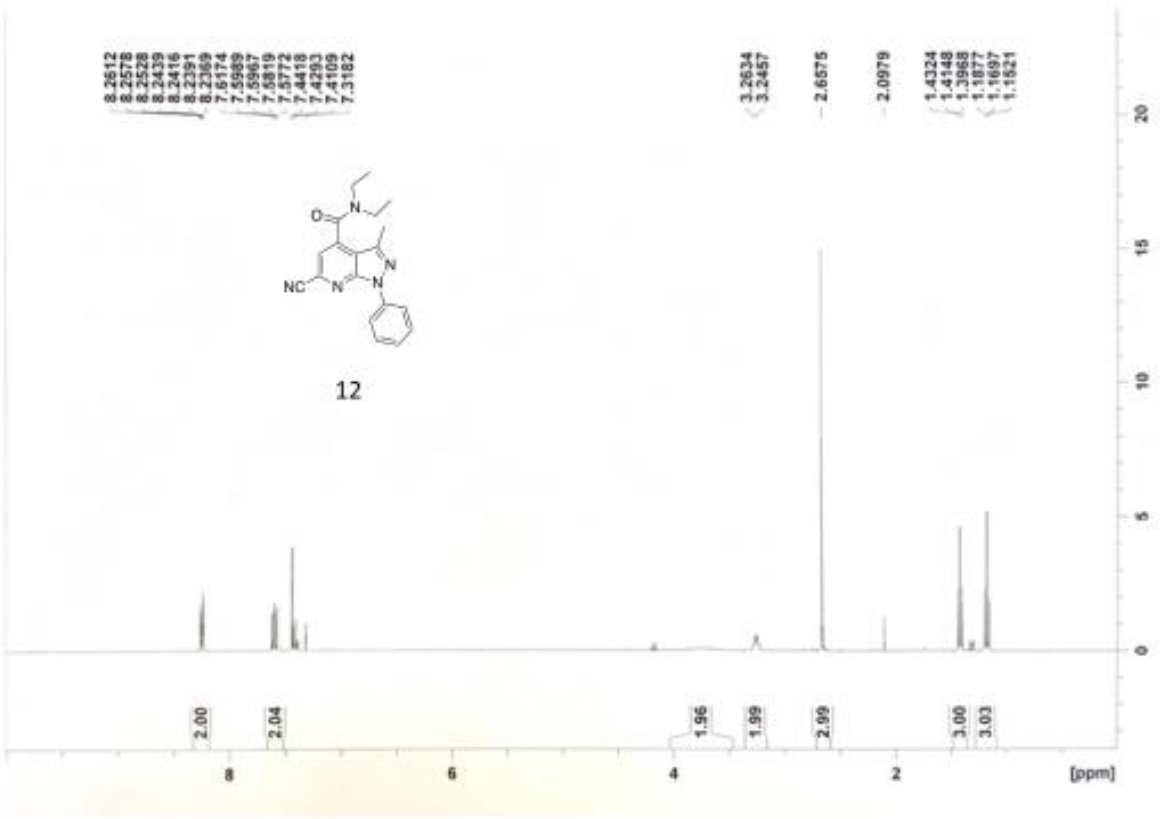
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7.4109
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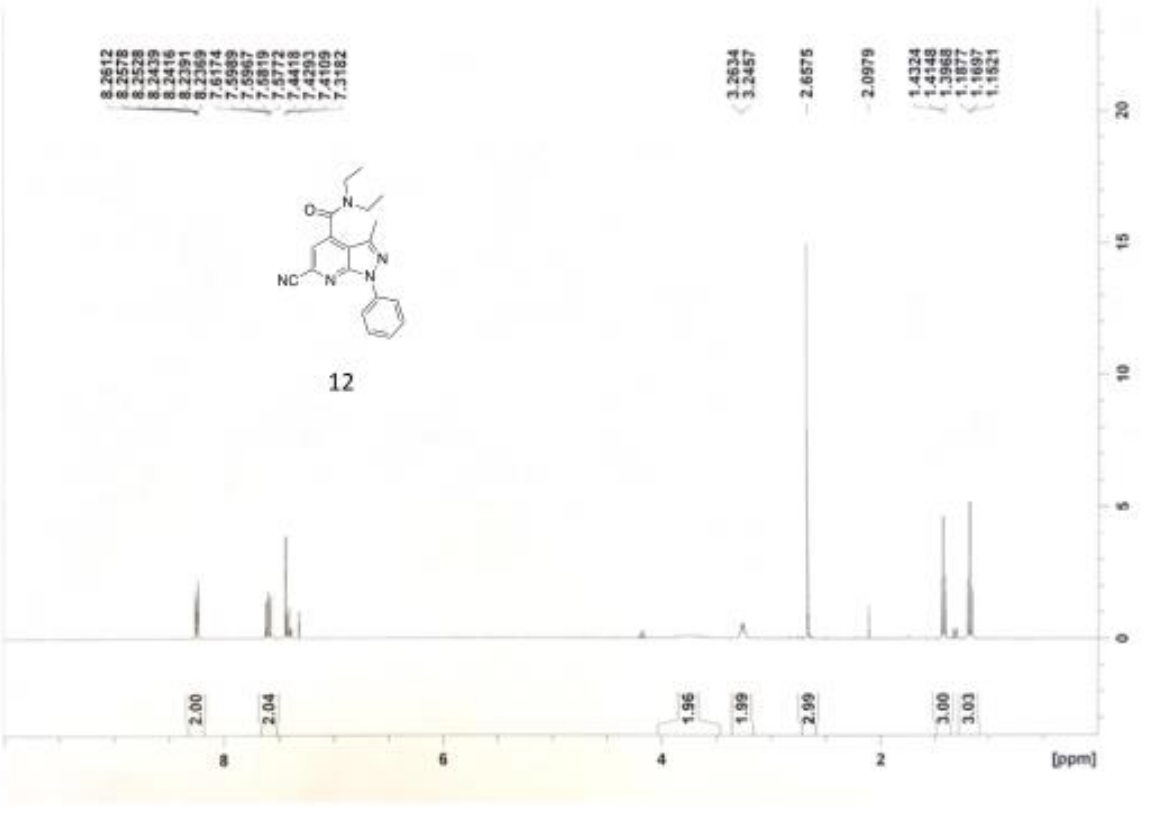
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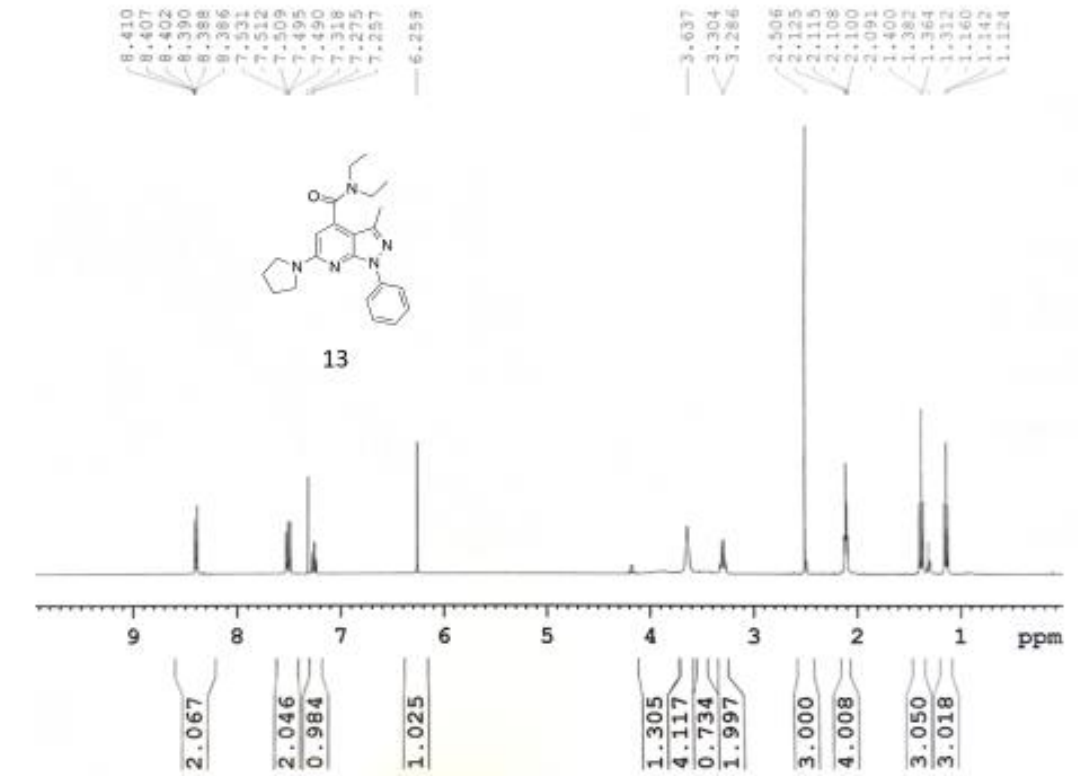
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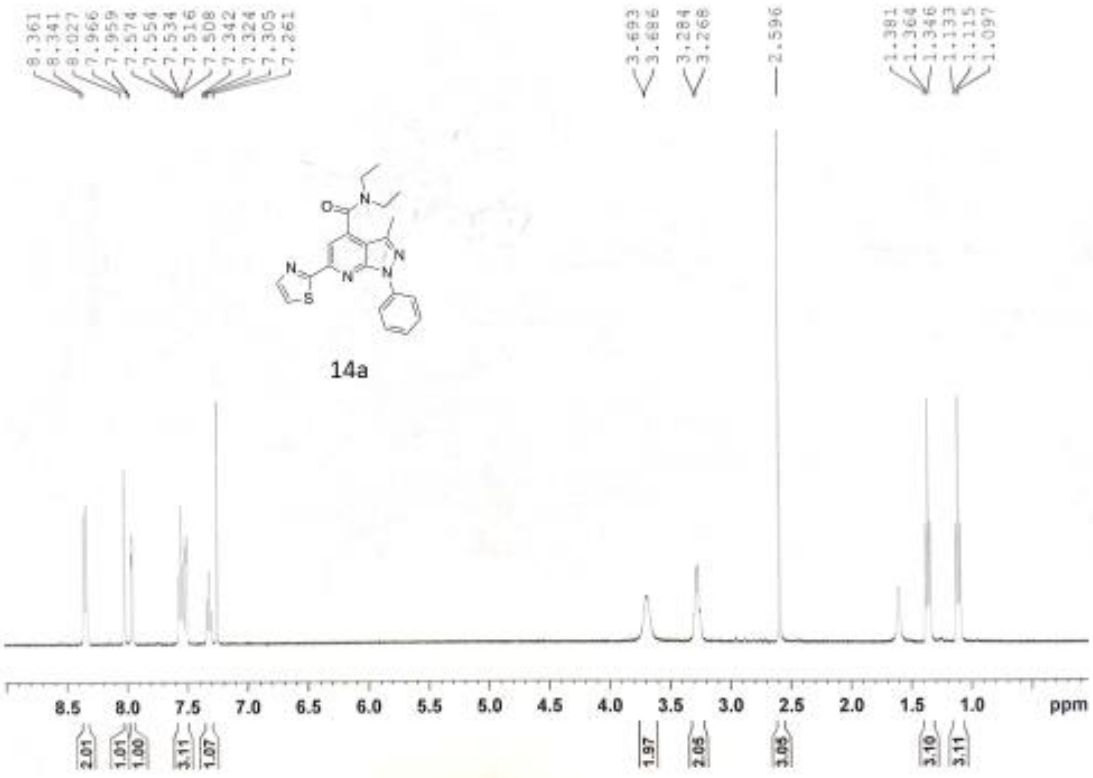
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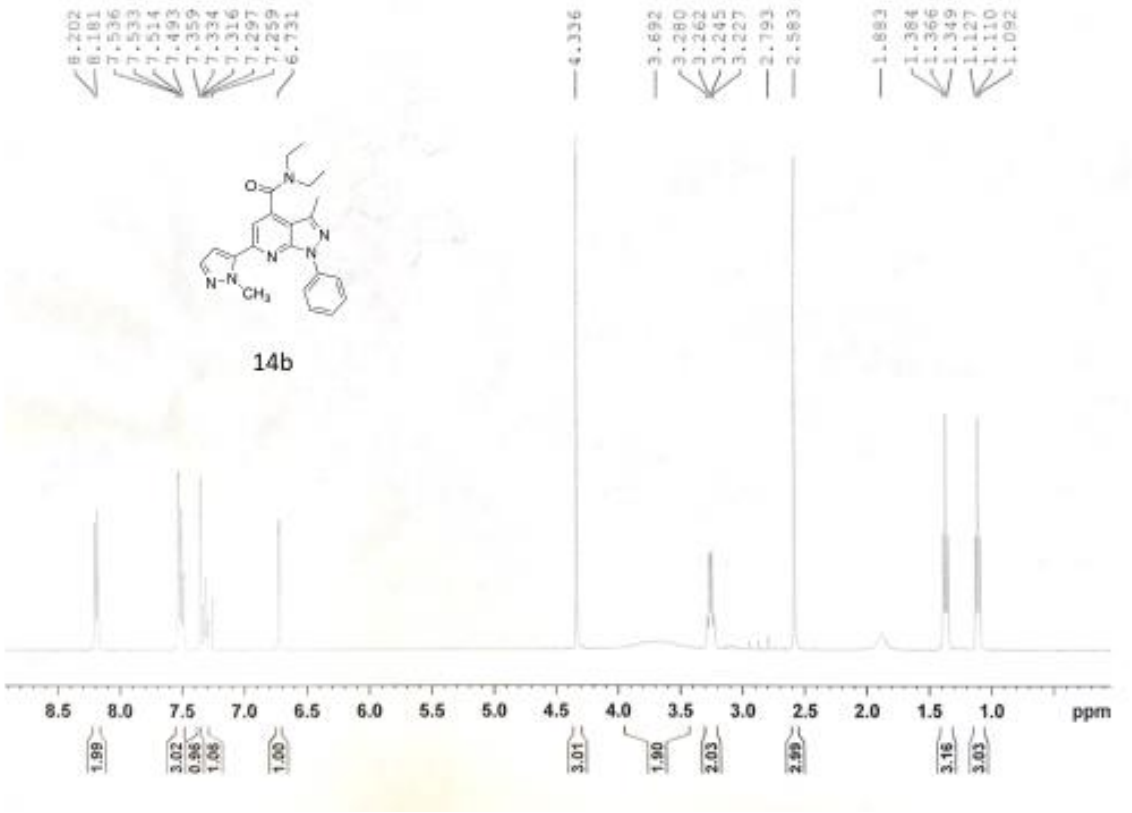
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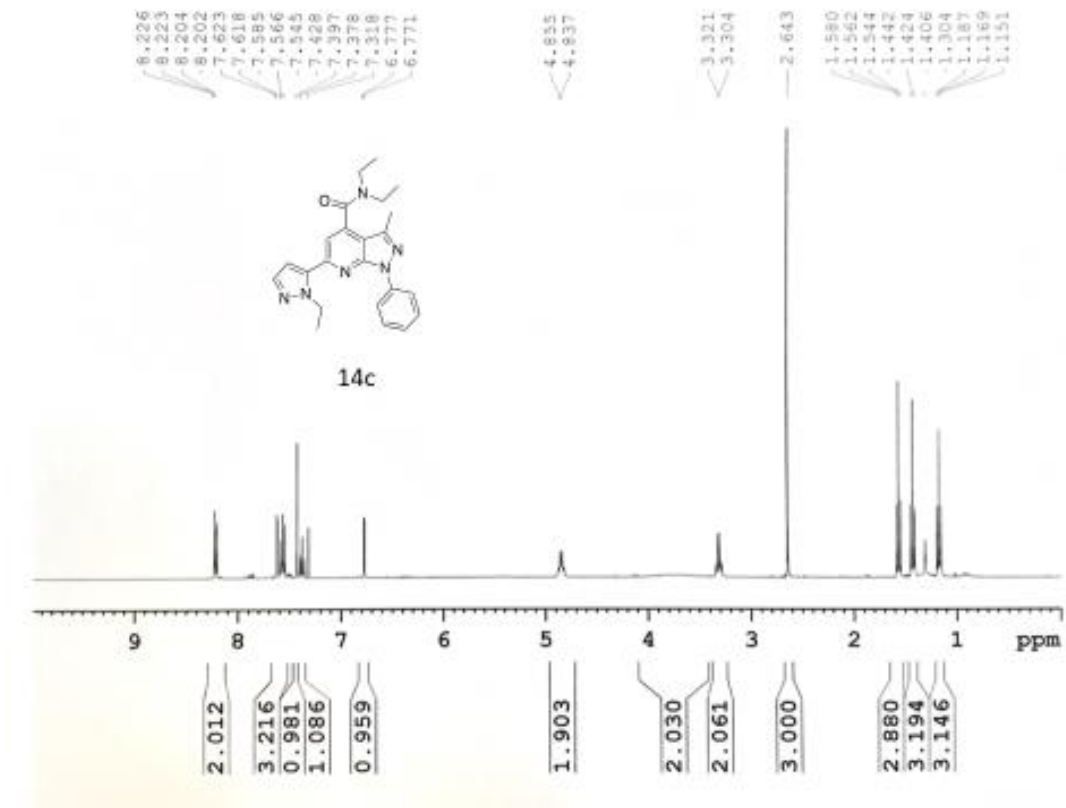
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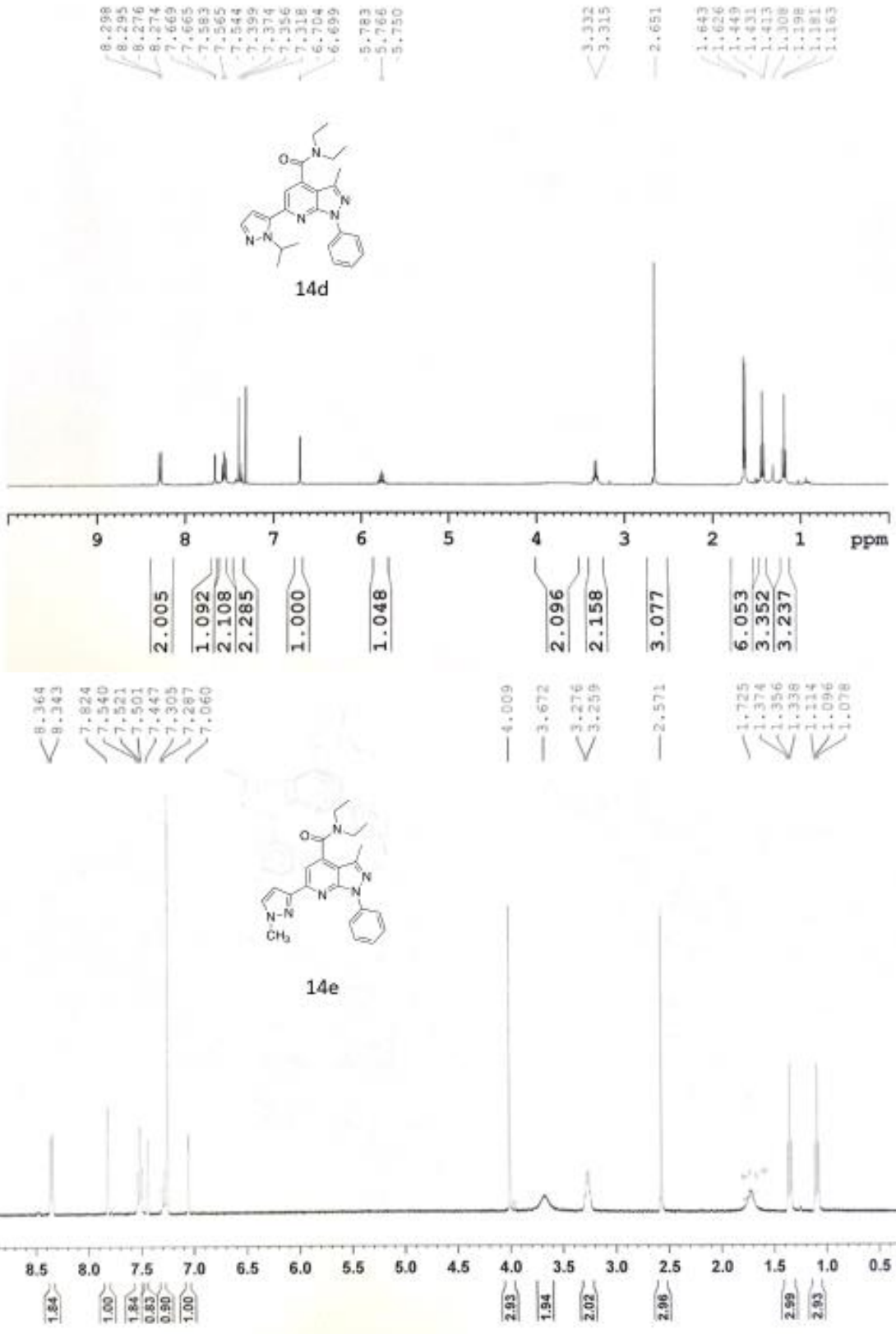
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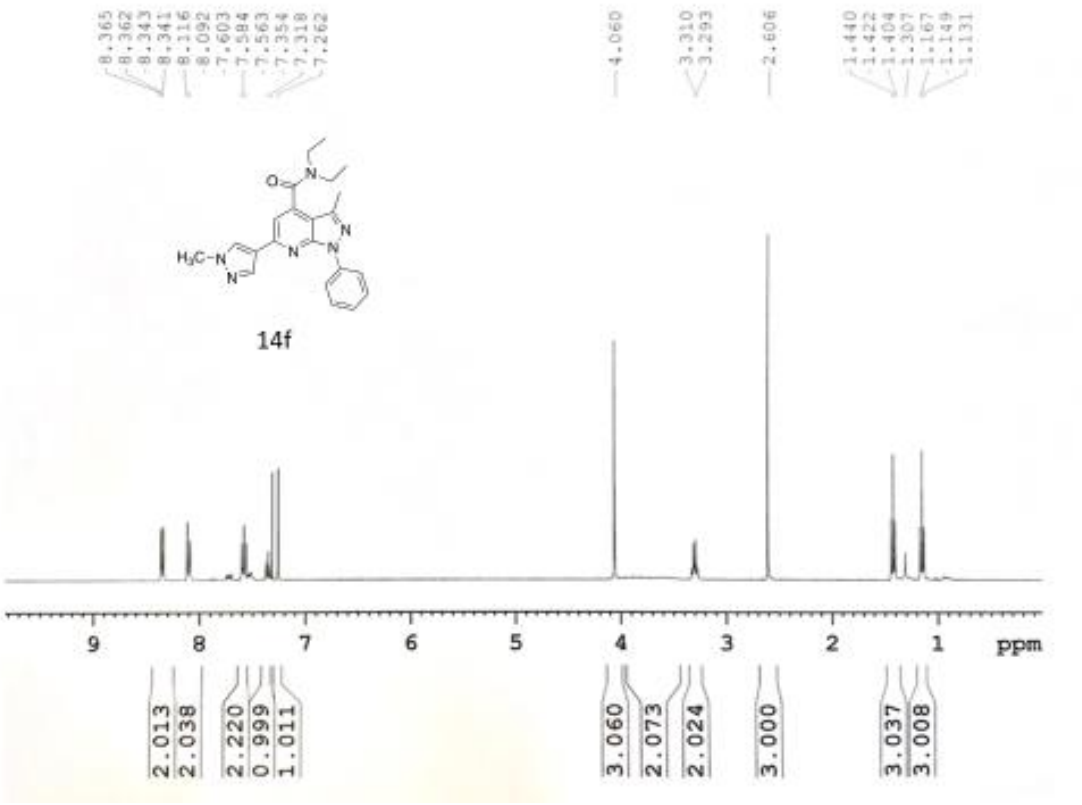
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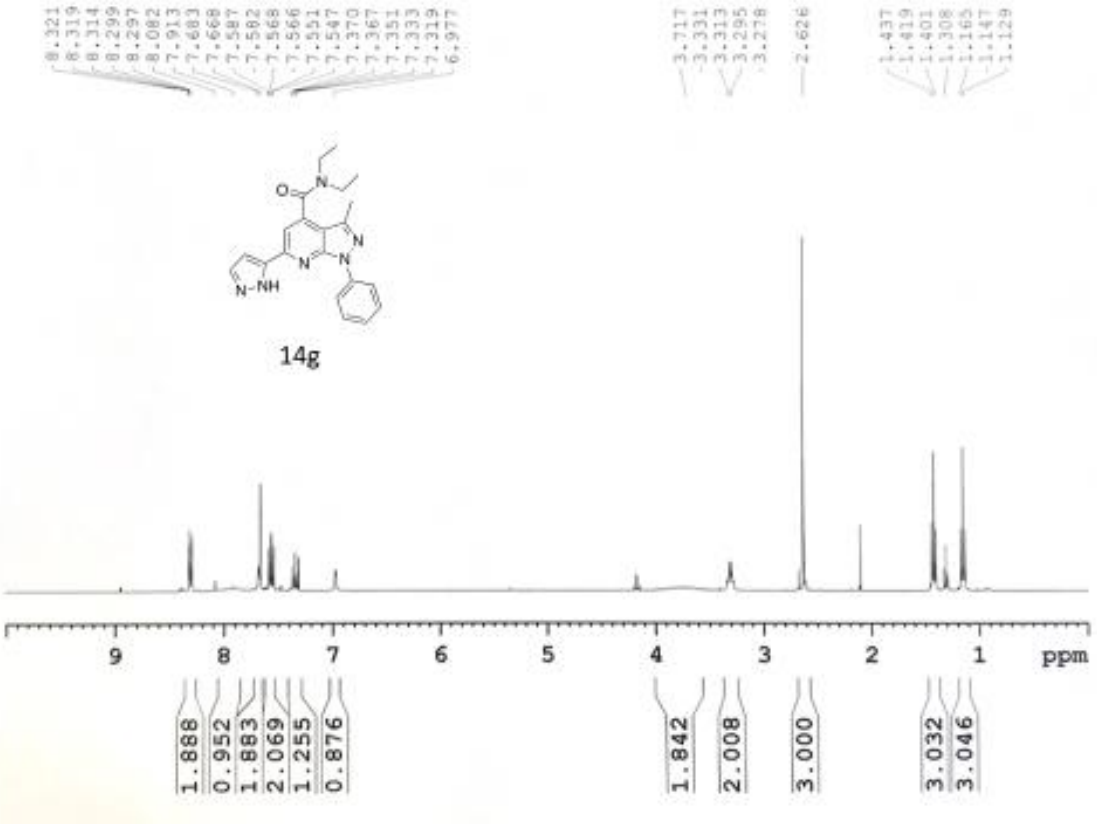
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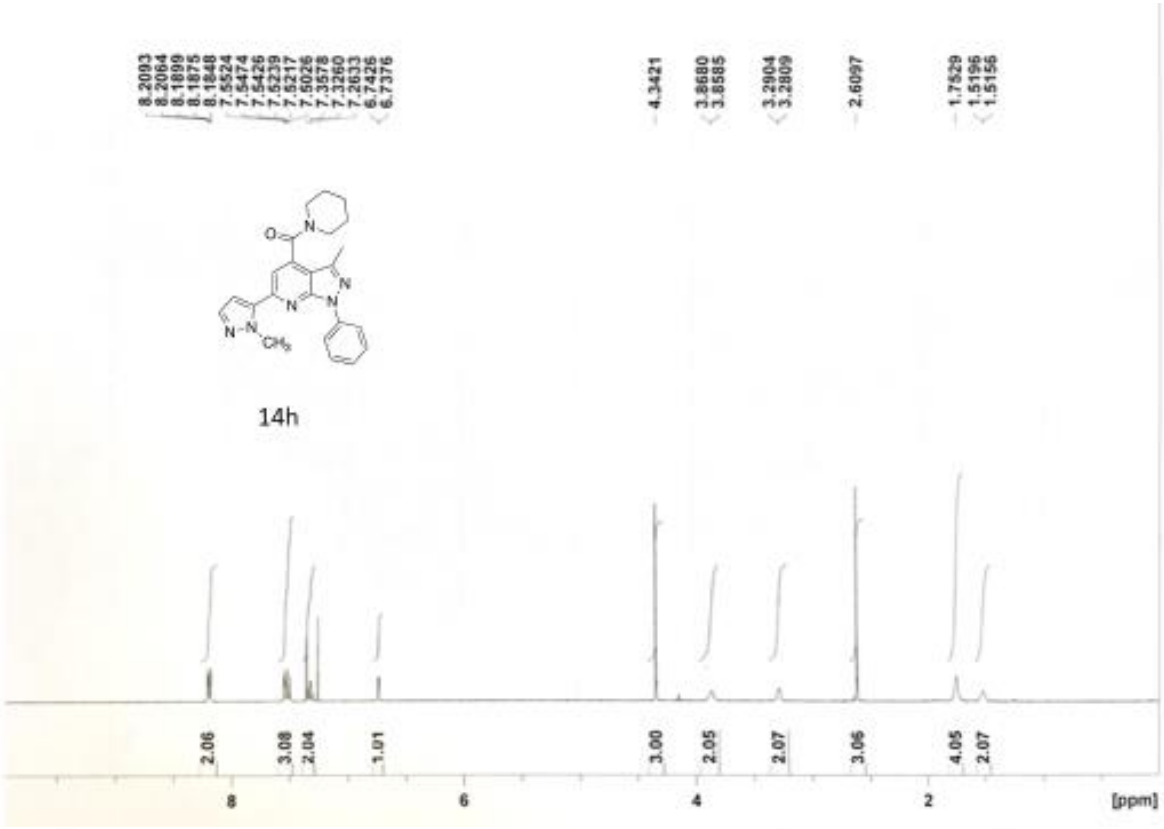
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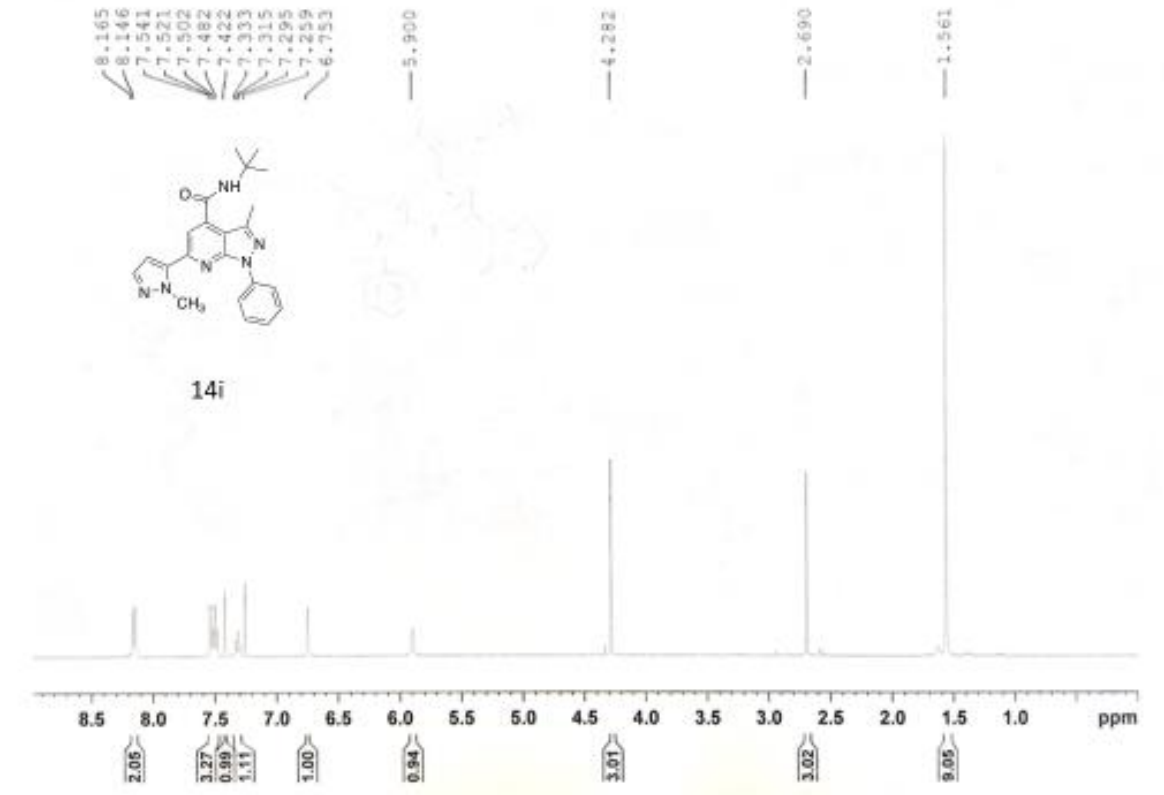
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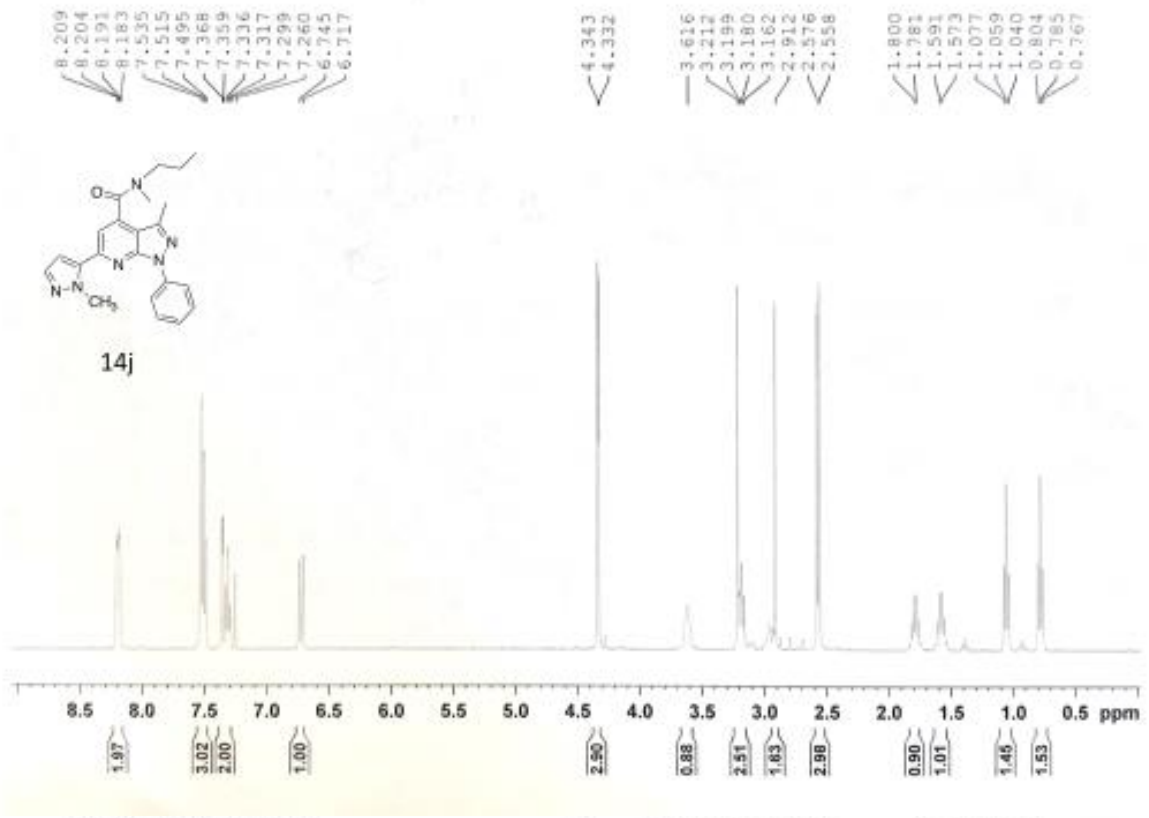
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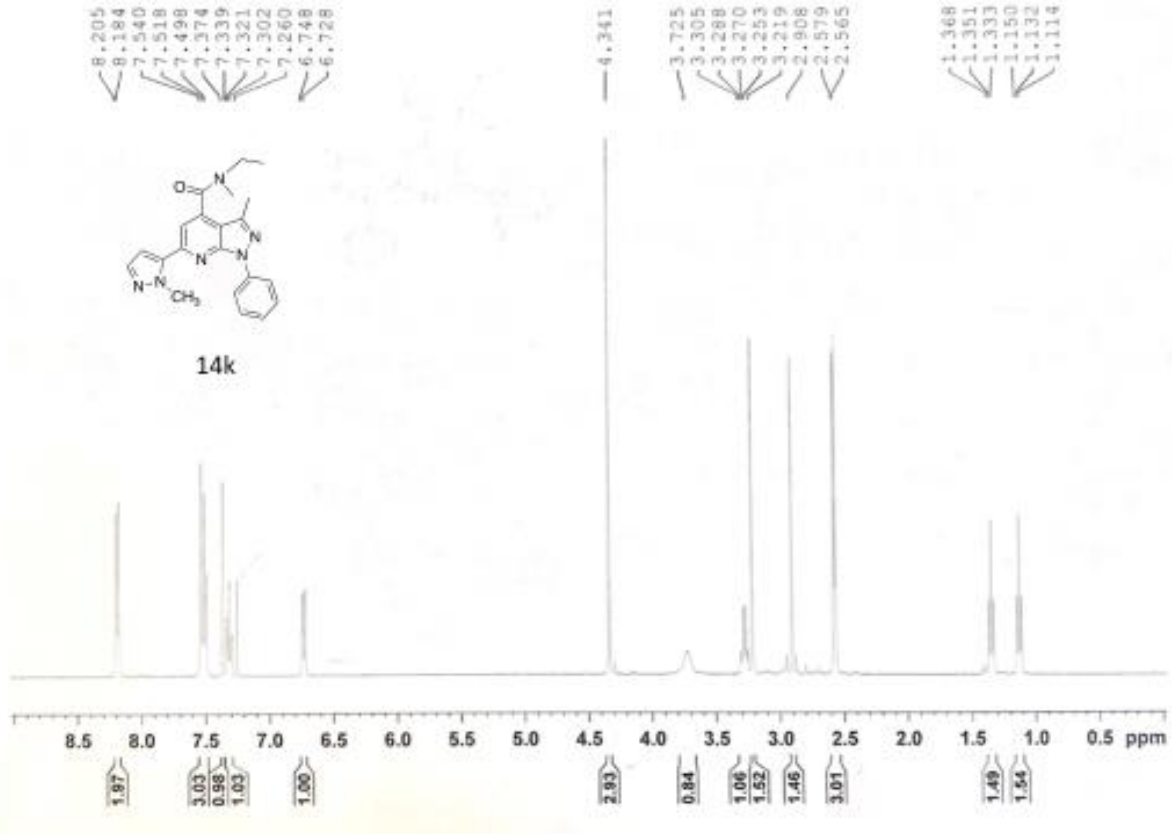
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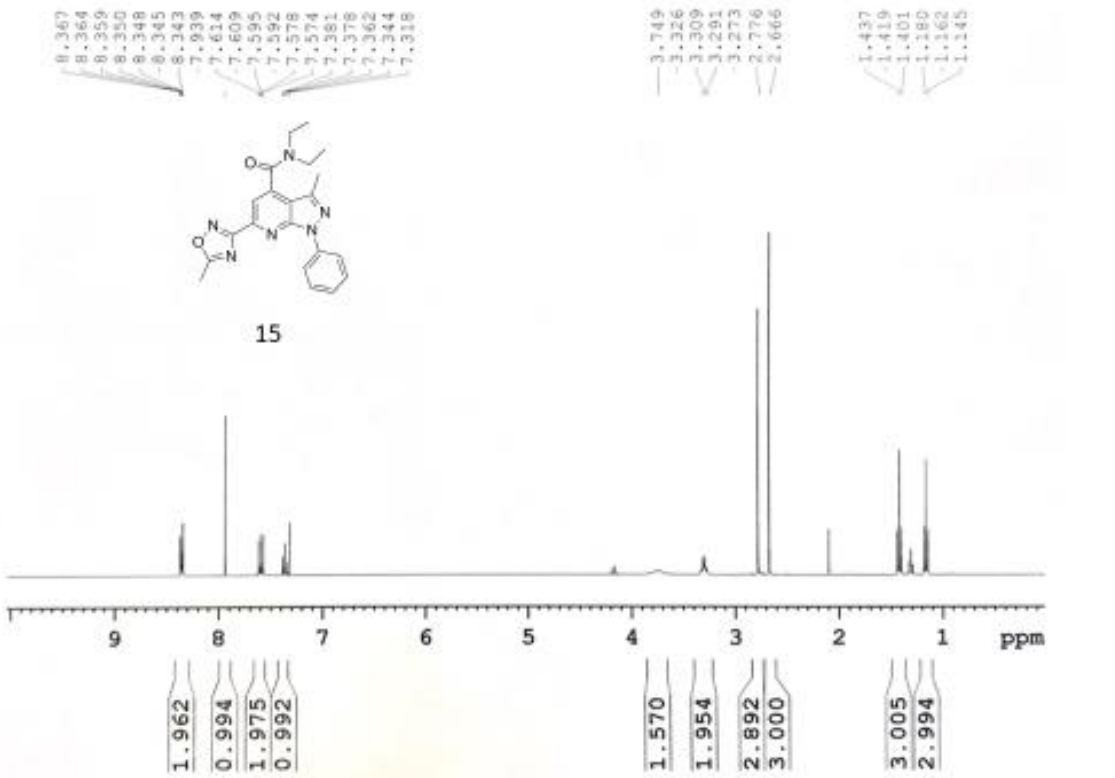
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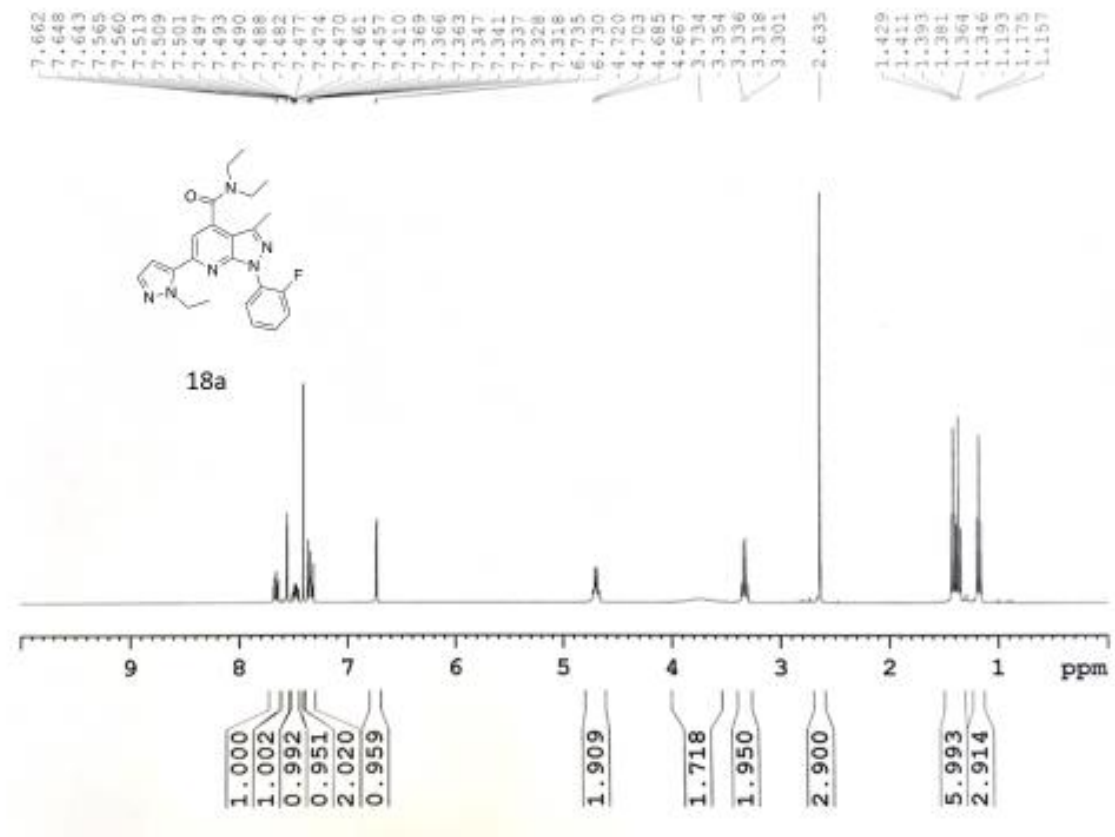
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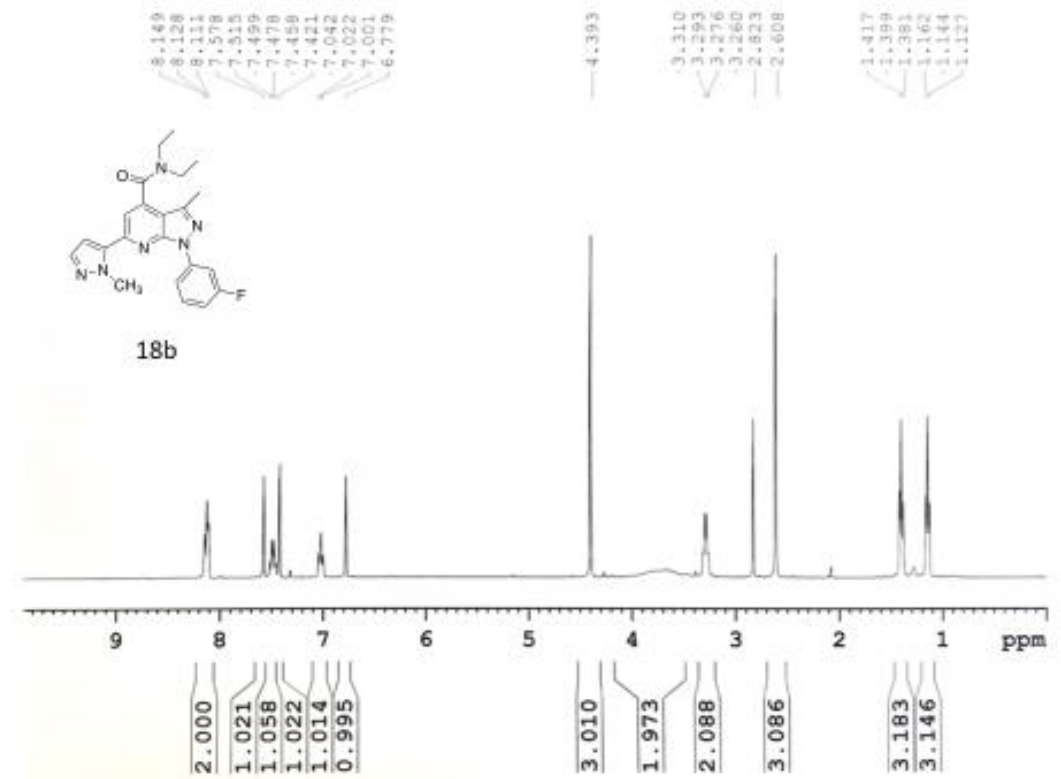
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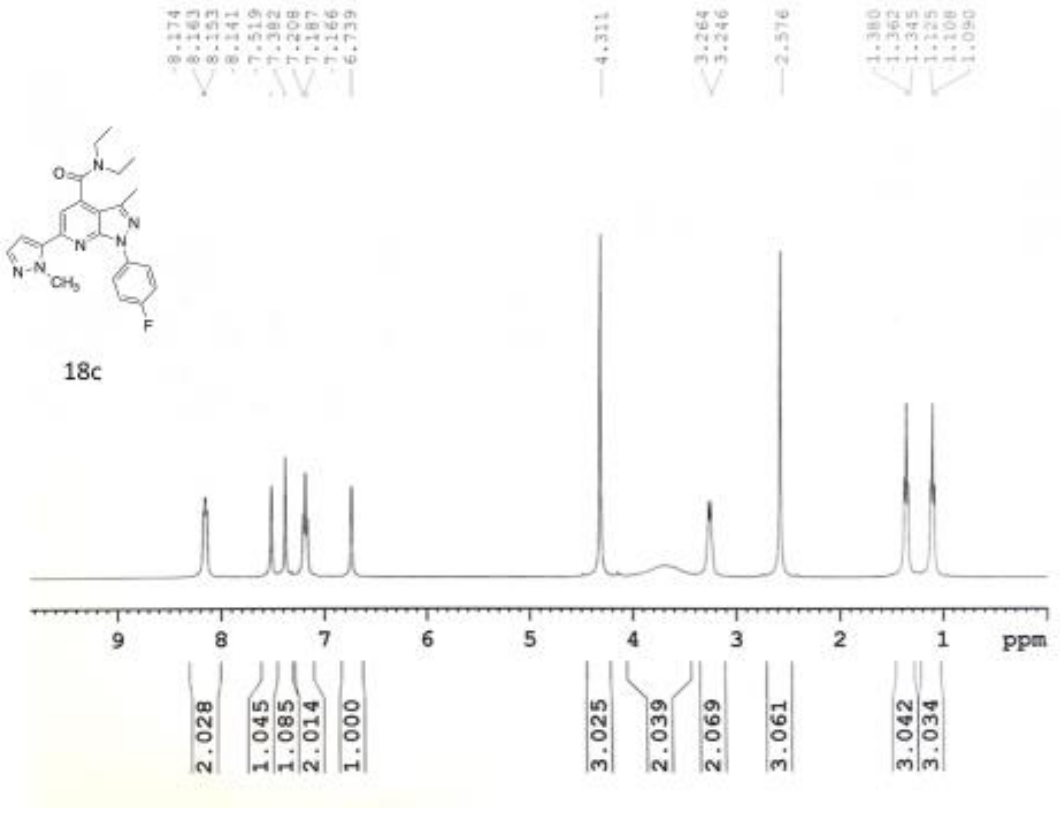
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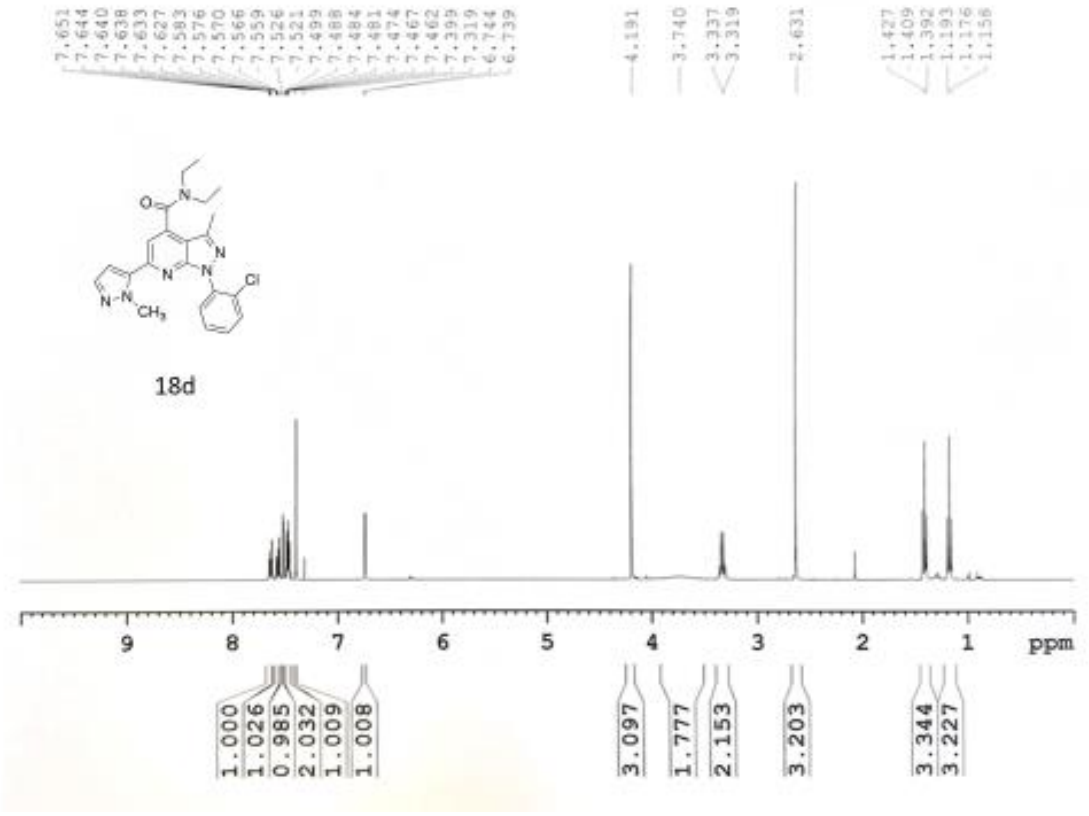
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7.583
7.576
7.570
7.566
7.559
7.526
7.521
7.499
7.488
7.484
7.481
7.474
7.467
7.462
7.399
7.319
6.744
6.739
4.191
3.740
3.337
3.319
2.631
1.427
1.409
1.392
1.193
1.176
1.158
18d
9
8
7
6
5
4
3
2
1
ppm
1.000
1.026
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2.032
1.009
1.008
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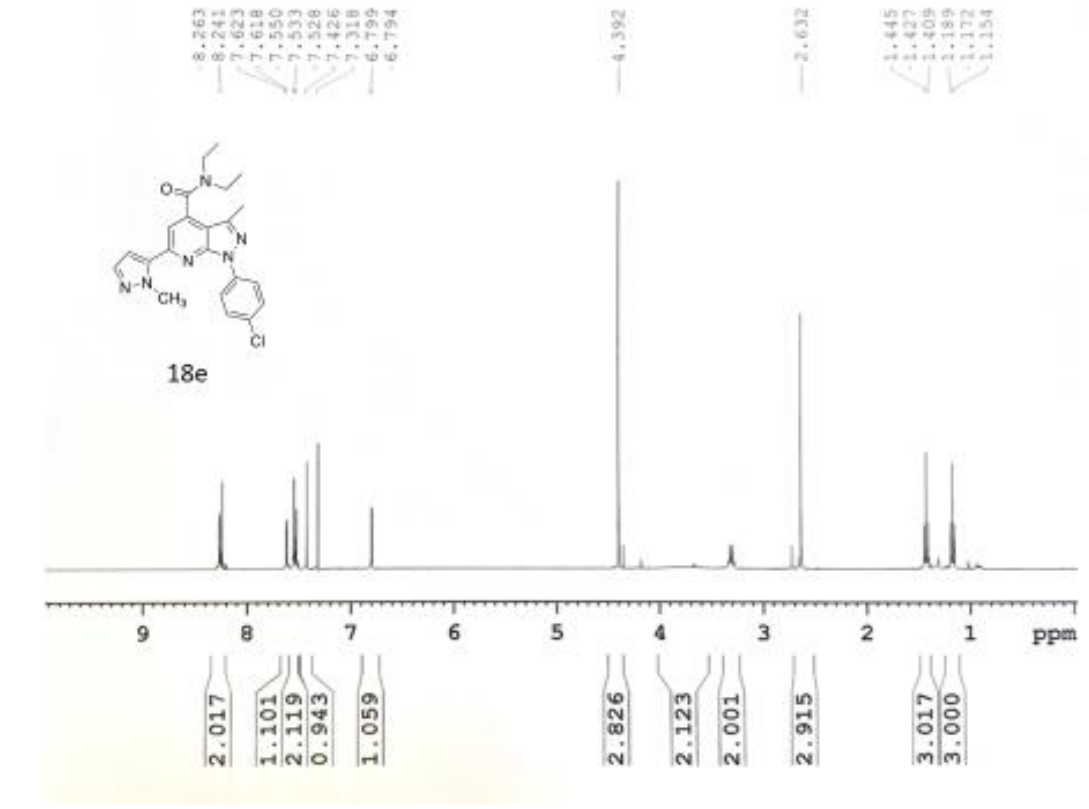
3.227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7.426
7.318
6.799
6.794
4.392
2.632
1.445
1.427
1.409
1.189
1.172
1.154
18e
9
8
7
6
5
4
3
2
1
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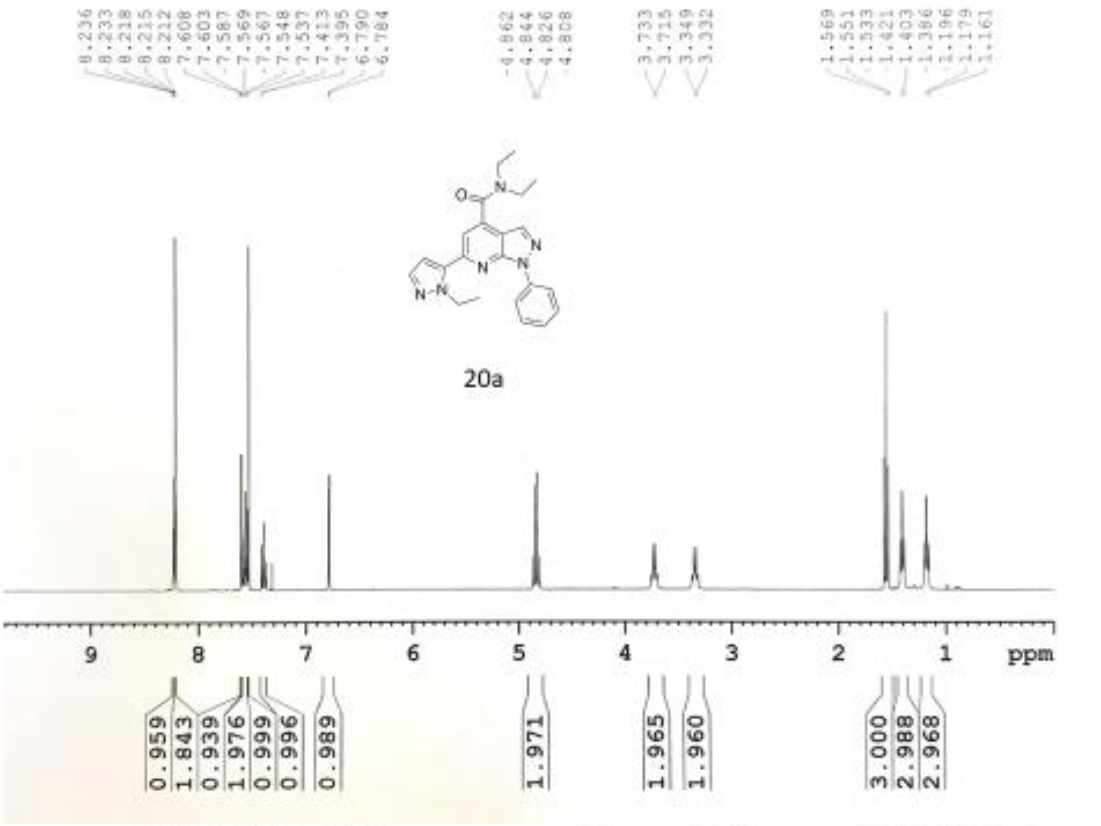
2.915
3.017
3.000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7.603
7.587
7.569
7.567
7.548
7.537
7.413
7.395
6.790
6.784
4.862
4.844
4.826
4.808
3.733
3.715
3.349
3.332
1.569
1.551
1.533
1.421
1.403
1.386
1.196
1.179
1.161
20a
9
8
7
6
5
4
3
2
1
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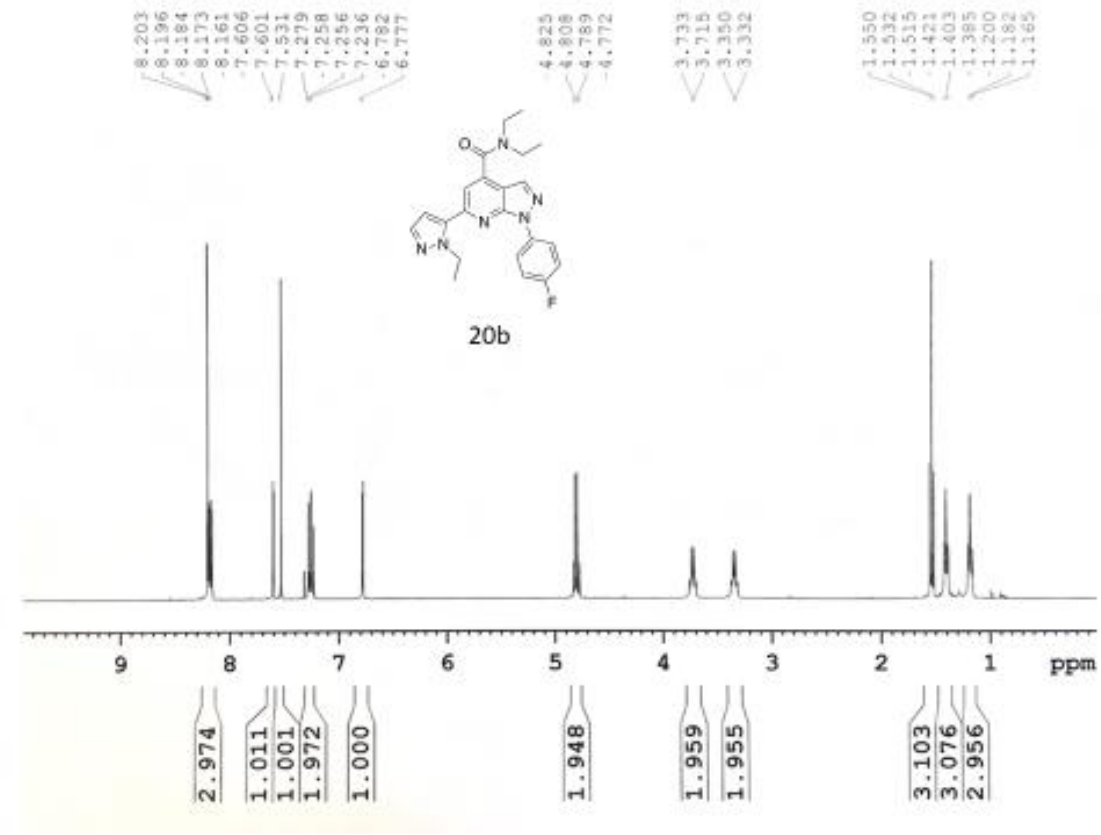
2.968


8.203
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8.173
8.161
7.606
7.601
7.531
7.279
7.258
7.256
7.236
6.782
6.777
4.825
4.808
4.789
4.772
3.733
3.715
3.350
3.332
1.550
1.532
1.515
1.421
1.403
1.385
1.200
1.182
1.165
20b
9
8
7
6
5
4
3
2
1
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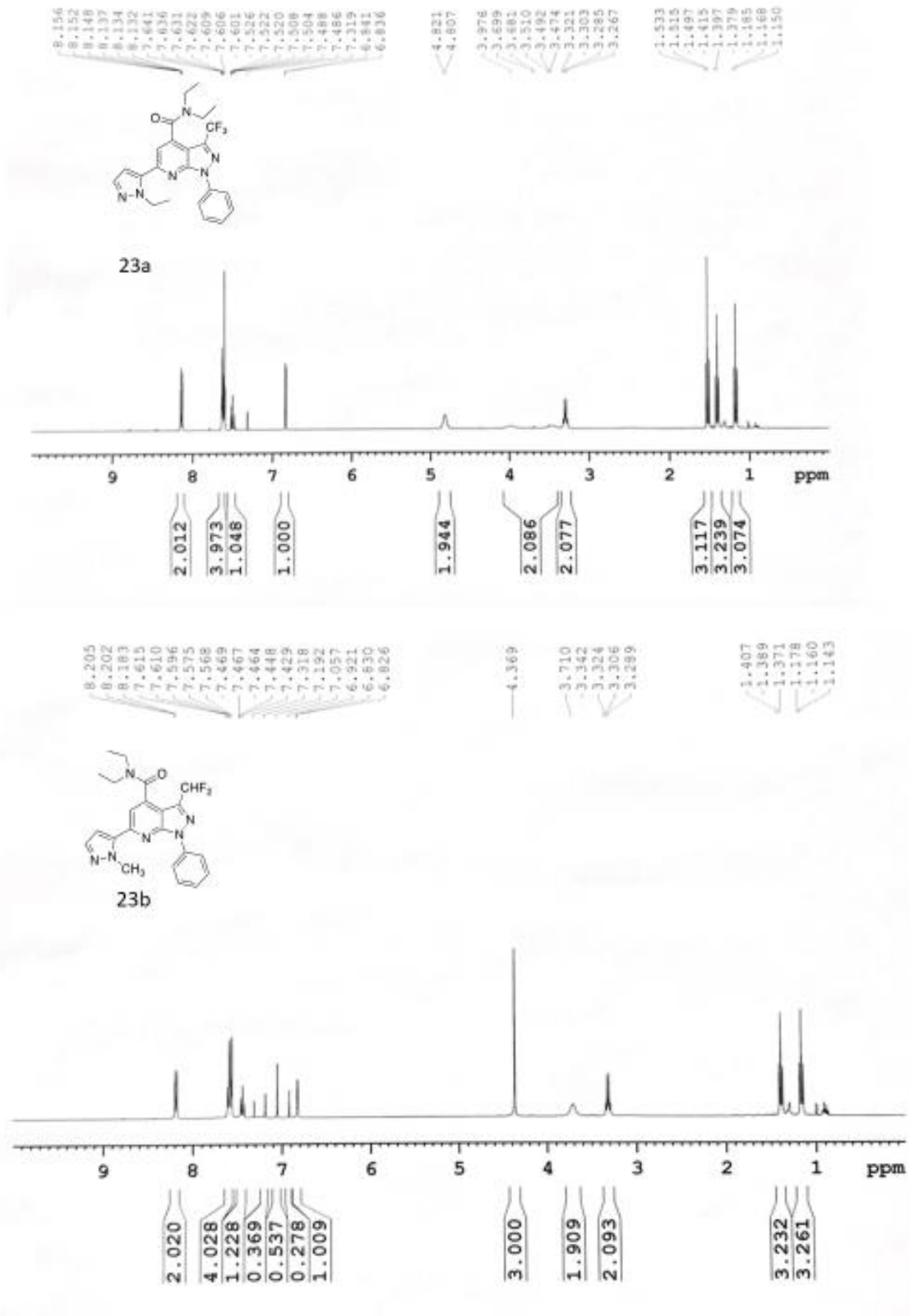
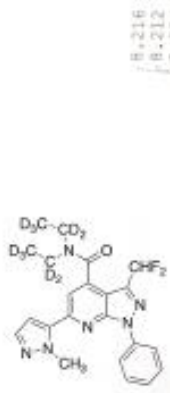
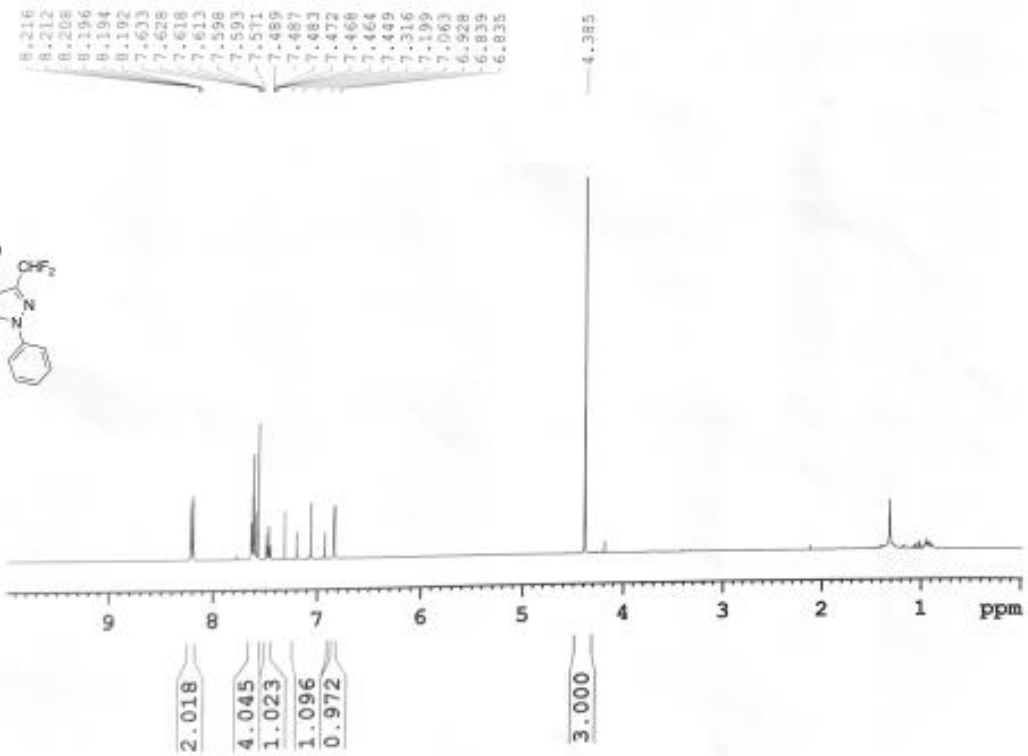
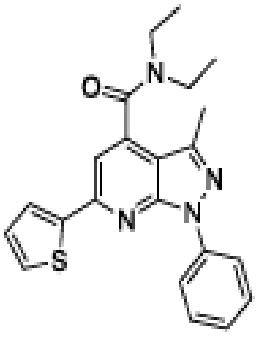
2.956


23a
23b
ppm

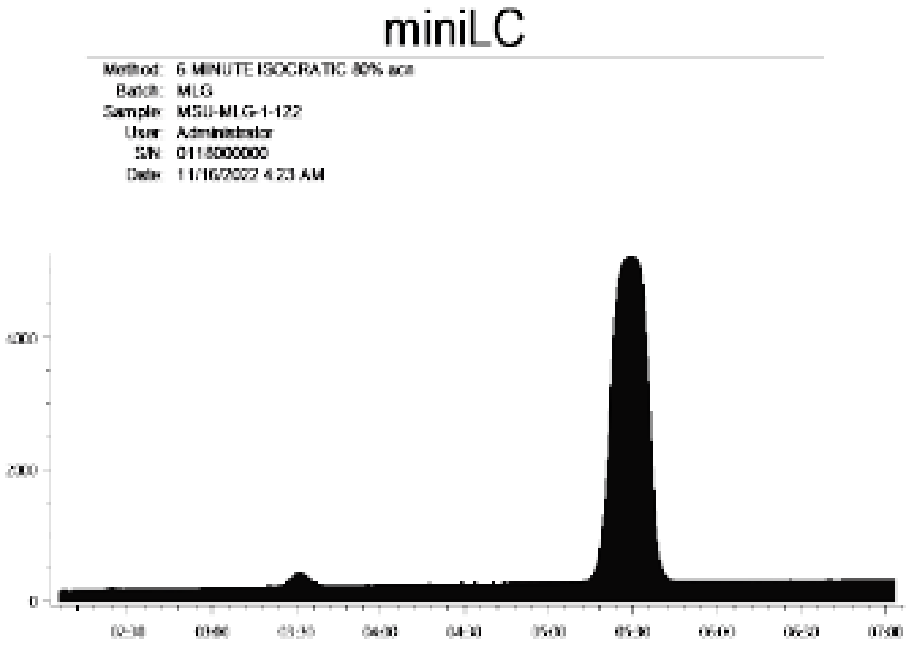


25

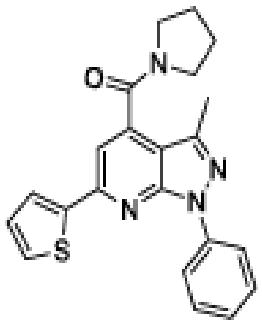




9a



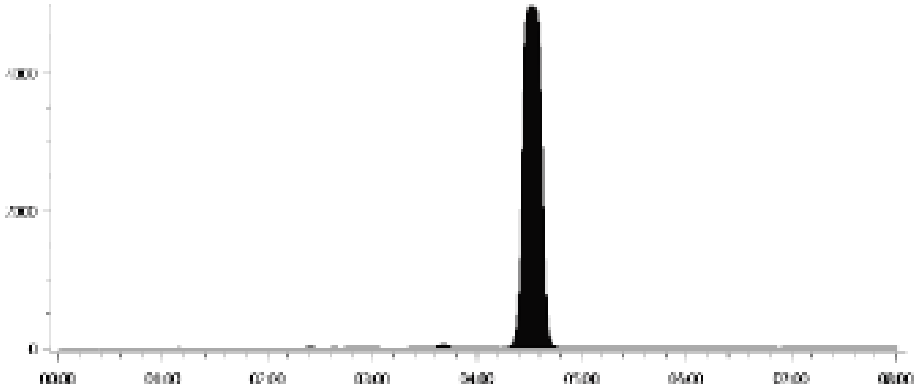
#	Compound	Retention Time	Area	% Area	Height
1		03.31 0	1320.8	1.8	1851.14
2		05.29.5	72168.3	98.2	4937.01



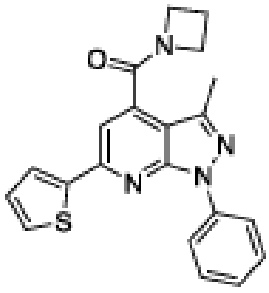
9b

miniLC

Method: 6 MINUTE ISOCRATIC 80% acn
Batch: BN
Sample: MSU-MLG-1-131
User: Administrator
S/N: 011M000000
Date: 11/16/2022 5:42 AM



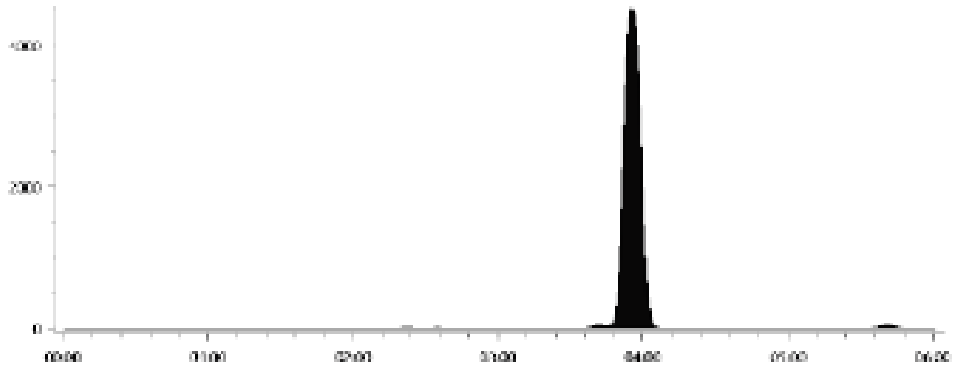
#	Compound	Retention Time	Area	% Area	Height
1		04.31.5	63515.5	100.0	4936.93



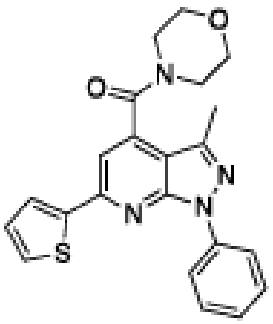
9c

miniLC

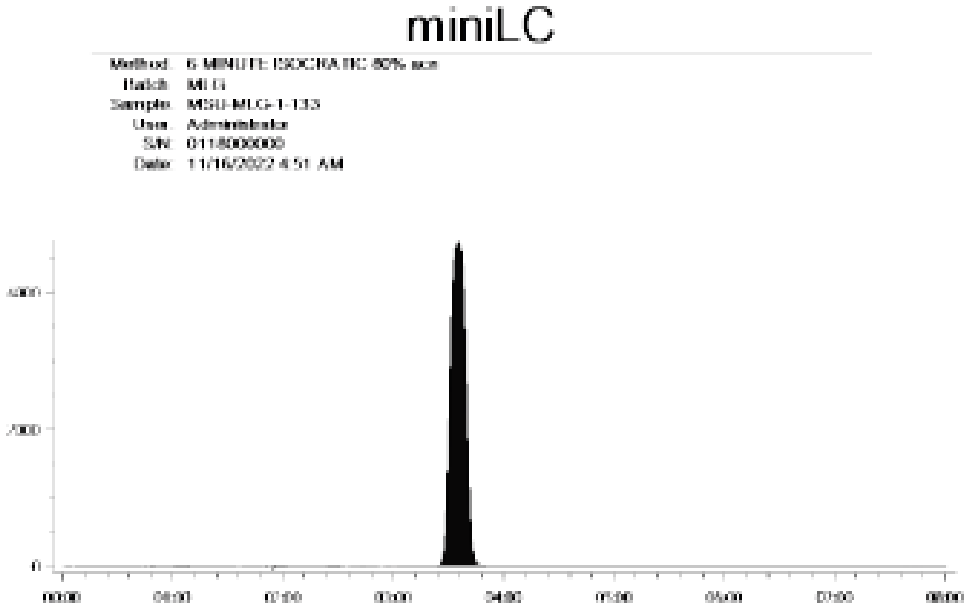
Method: 6 MINUTE ISOCRATIC 80% acn
Batch: LK
Sample: MSU-MLG-1-132
User: Guest
S/N: 011M000000
Date: 11/30/2022 4:39 AM



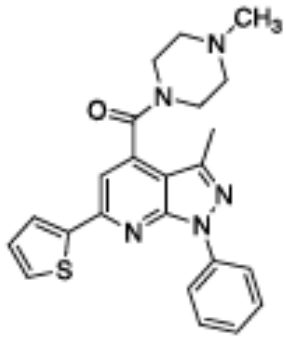
#	Compound	Retention Time	Area	% Area	Height
1		03.55.5	37985.3	98.6	4519.82
2		05.41.0	492.1	1.4	61.12



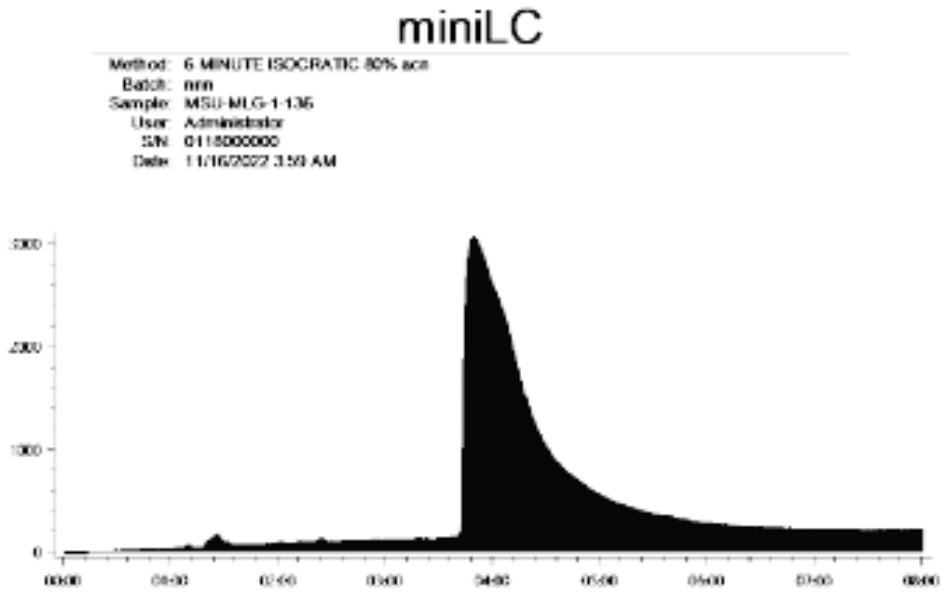
9d



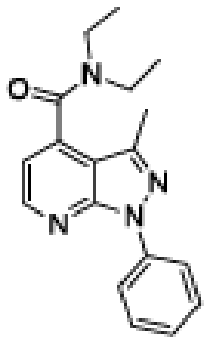
#	Compound	Retention Time	Area	% Area	Height
1		03:35.5	45196.0	100.0	4751.95



9e



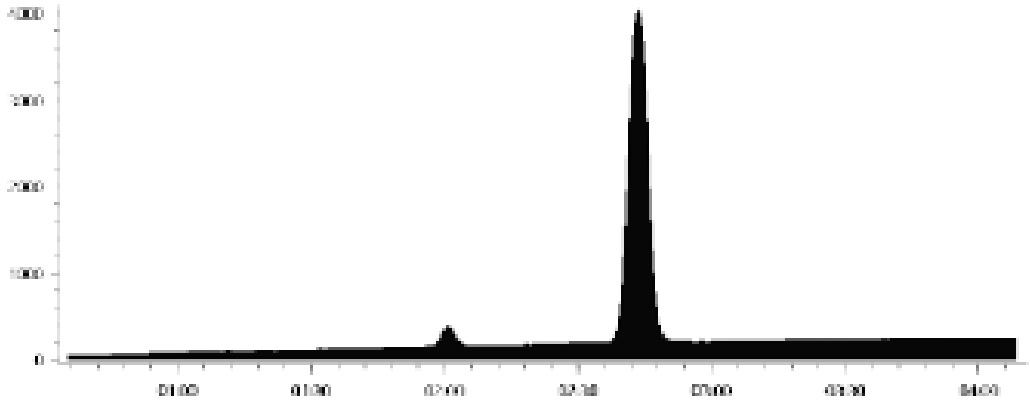
#	Compound	Retention Time	Area	% Area	Height
1		03:50.5	139136.0	100.0	2961.82



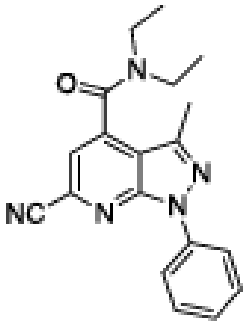
11

miniLC

Method: 6 MINUTE ISOCRATIC 80% acn
Batch: BN
Sample: MSU-MLG-1-121
User: Administrator
S/N: 0118000000
Date: 11/16/2022 5:32 AM



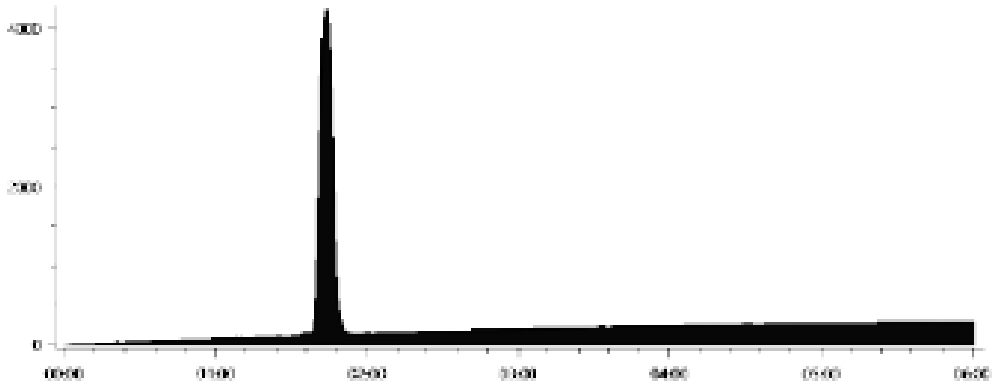
#	Compound	Retention Time	Area	% Area	Height
1		02.07.0	748.7	3.8	229.40
2		02.43.5	19088.3	96.2	3840.73



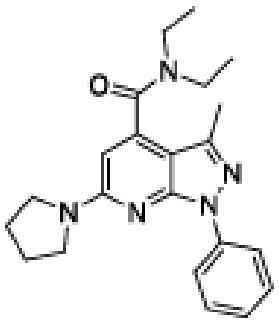
12

miniLC

Method: 6 MINUTE ISOCRATIC 80% acn
Batch: BNN
Sample: MSU-TSR-1-32
User: Guest
S/N: 0118000000
Date: 11/30/2022 12:52 AM



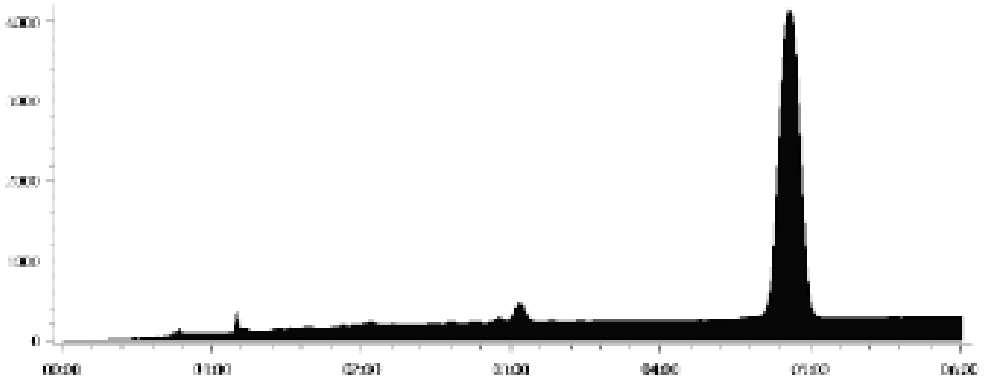
#	Compound	Retention Time	Area	% Area	Height
1		01.44.0	37209.5	100.0	4108.69



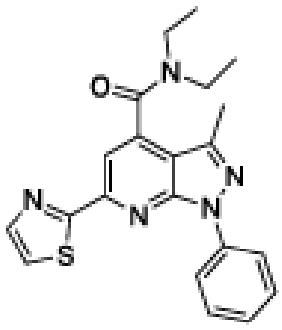
13

miniLC

Method: 6 MINUTE ISOCRATIC 80% acn
Batch: UV
Sample: MSU-ESR-1-62
User: Guest
S/N: 011B000000
Date: 11/30/2022 12:08 AM



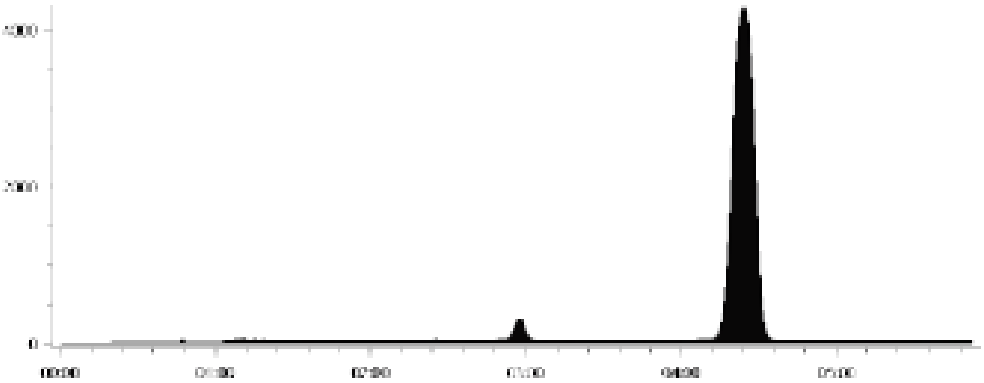
#	Compound	Retention Time	Area	% Area	Height
1		01:12.0	396.6	1.1	50.53
2		03:03.5	1016.7	2.7	231.62
3		04:52.0	35902.2	96.2	3874.36



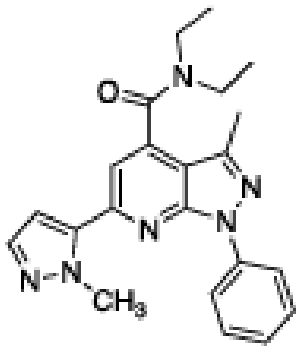
14a

miniLC

Method: 6 MINUTE ISOCRATIC 80% acn
Batch: MLG-SECOND
Sample: MSU-MLG-1-169
User: Administrator
S/N: 011B000000
Date: 11/16/2022 11:59 PM



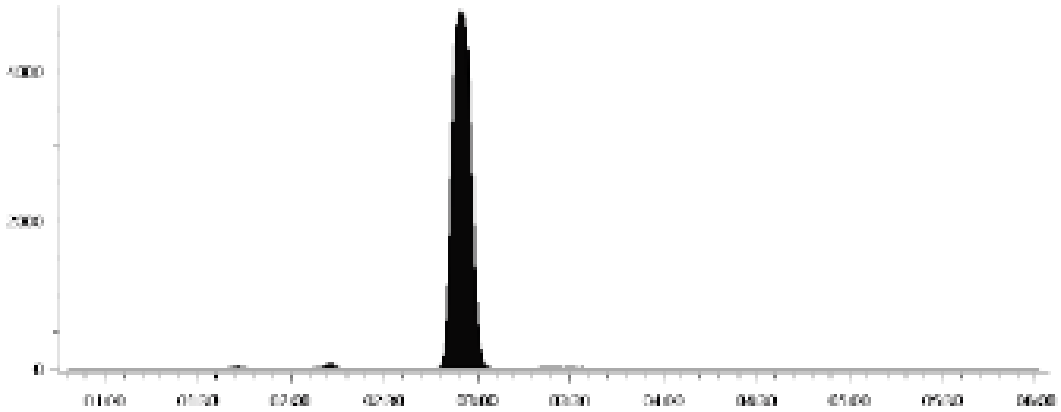
#	Compound	Retention Time	Area	% Area	Height
1		02:57.5	4367.1	3.3	289.64
2		04:24.0	89638.6	96.7	4243.10



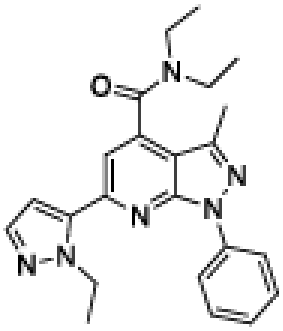
14b

miniLC

Method: 6 MINUTE ISOCRATIC 80% acn
Batch: LK
Sample: MSU-MLG-1-185
User: Guest
S/N: 0118000000
Date: 11/30/2022 4:47 AM



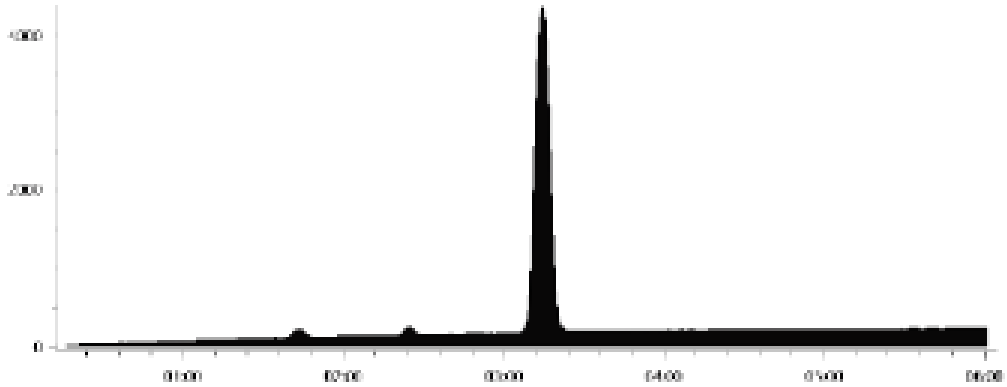
#	Compound	Retention Time	Area	% Area	Height
1		02.12.5	347.6	1.0	79.46
2		02.55.0	32596.9	99.0	4797.49



14c

miniLC

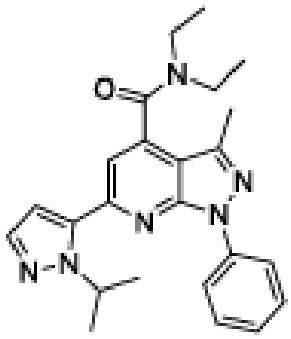
Method: 6 MINUTE ISOCRATIC 80% acn
Batch: LK
Sample: MSU-TSR-1-57
User: Guest
S/N: 0118000000
Date: 11/30/2022 4:24 AM

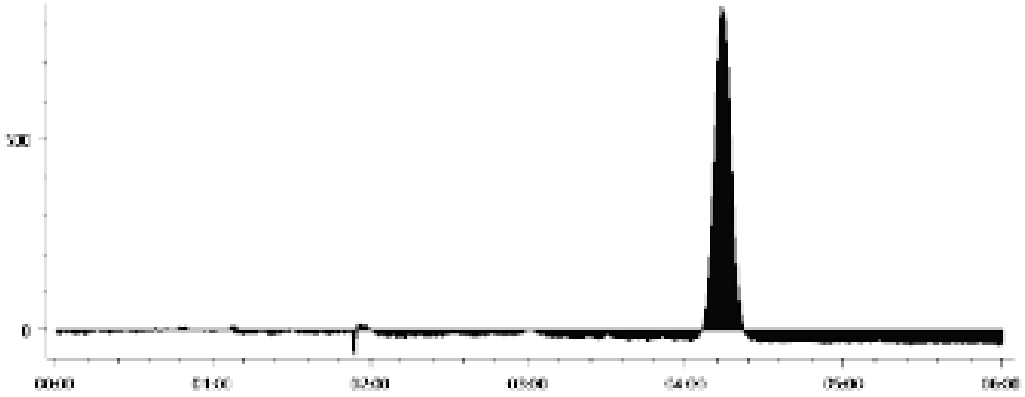


#	Compound	Retention Time	Area	% Area	Height
1		01.44.0	472.8	1.7	95.89
2		02.24.5	337.0	1.2	88.37
3		03.14.5	27391.2	97.0	4140.54

miniLC

Method: 6 MINUTE ISOCRATIC 80% acn
Batch: KJ
Sample: MSU-TSR-1-54
User: Administrator
S/N: 011B000000
Date: 11/29/2022 1:04 AM



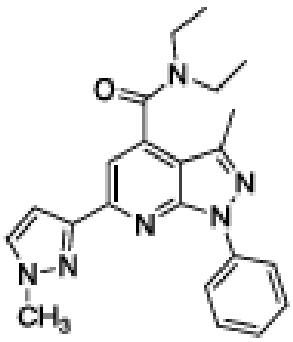


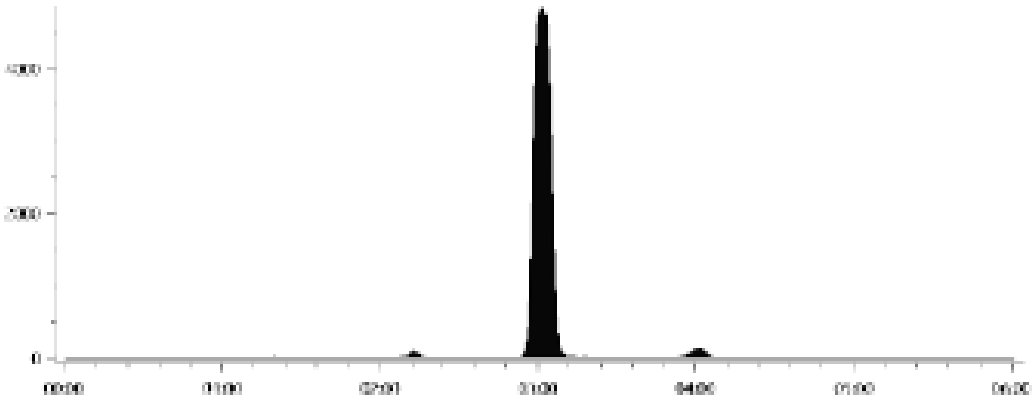
14d

#	Compound	Retention Time	Area	% Area	Height
1		04:14.0	8133.1	100.0	863.94

miniLC

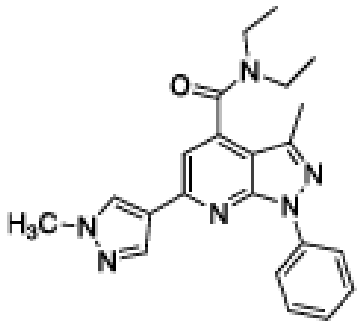
Method: 6 MINUTE ISOCRATIC 80% acn
Batch: LK
Sample: MSU-MLG-1-189
User: Guest
S/N: 011B000000
Date: 11/30/2022 4:31 AM



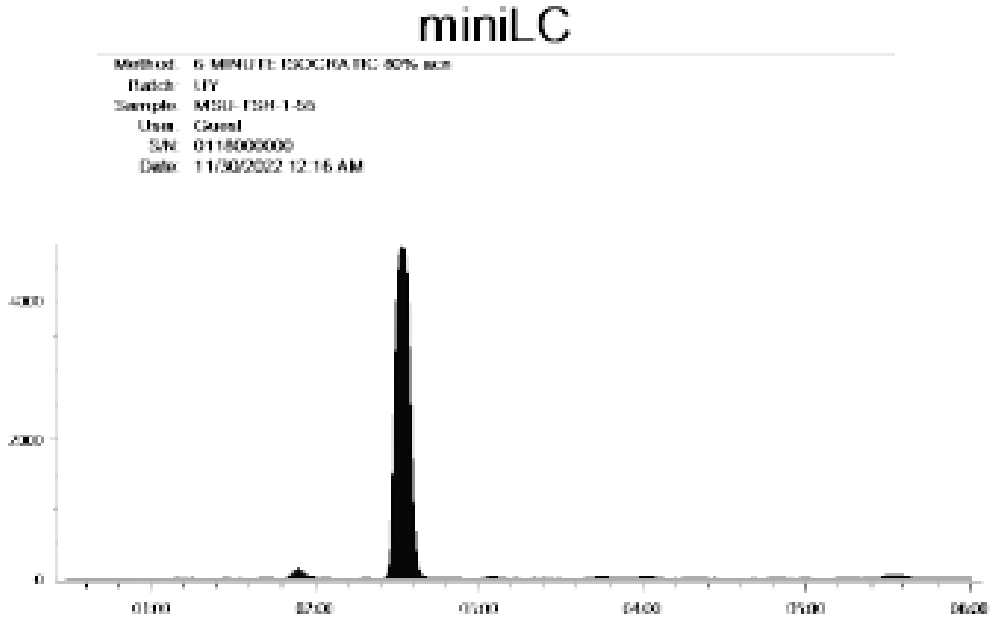


14e

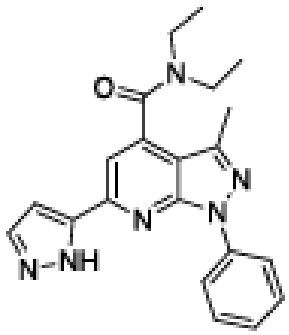
#	Compound	Retention Time	Area	% Area	Height
1		02:13.0	816.6	1.0	99.65
2		03:01.5	353/0.5	96.7	4817.22
3		04:00.5	800.4	2.3	131.12



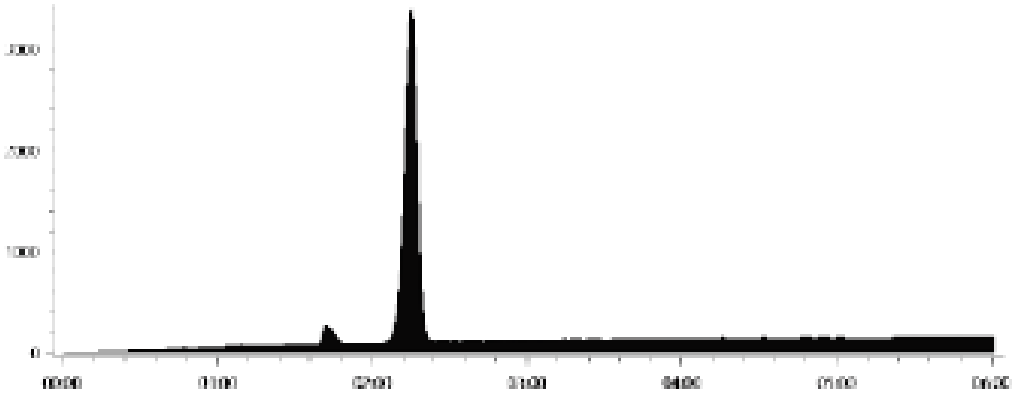
14f



#	Compound	Retention Time	Area	% Area	Height
1		01:54.5	545.1	1.8	123.34
2		02:32.0	30351.4	96.6	4796.92
3		05:32.5	426.0	1.4	91.36



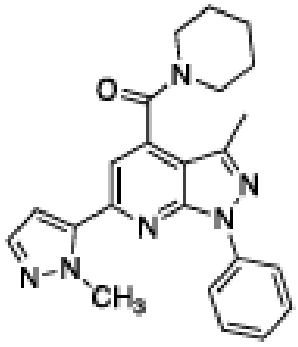
14g

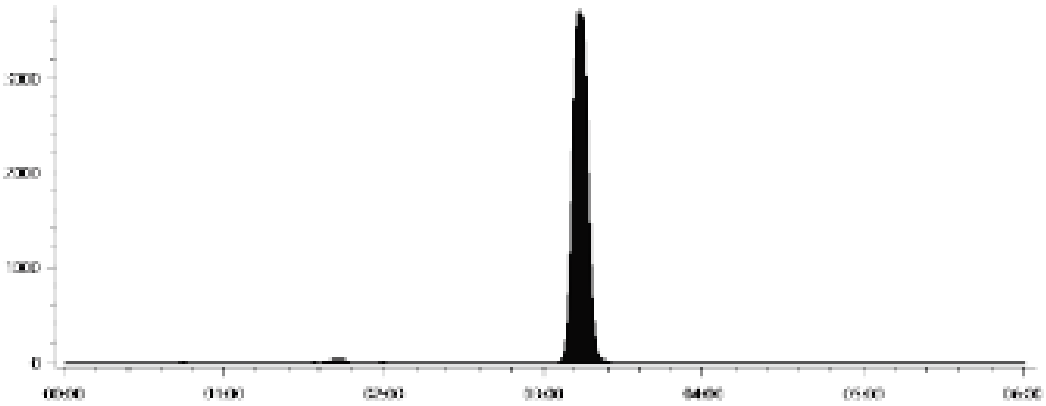


#	Compound	Retention Time	Area	% Area	Height
1		01:43.0	784.0	3.7	194.81
2		02:15.5	19772.4	96.3	3252.82

miniLC

Method: 6 MINUTE ISOCRATIC 80% acn
Batch: UY
Sample: MSU-TSR-1-3
User: Guest
S/N: 0118000000
Date: 11/30/2022 12:31 AM



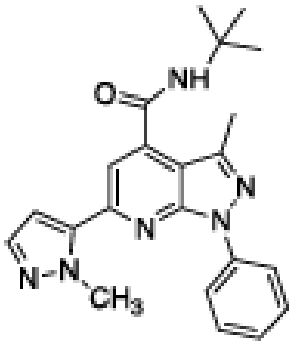


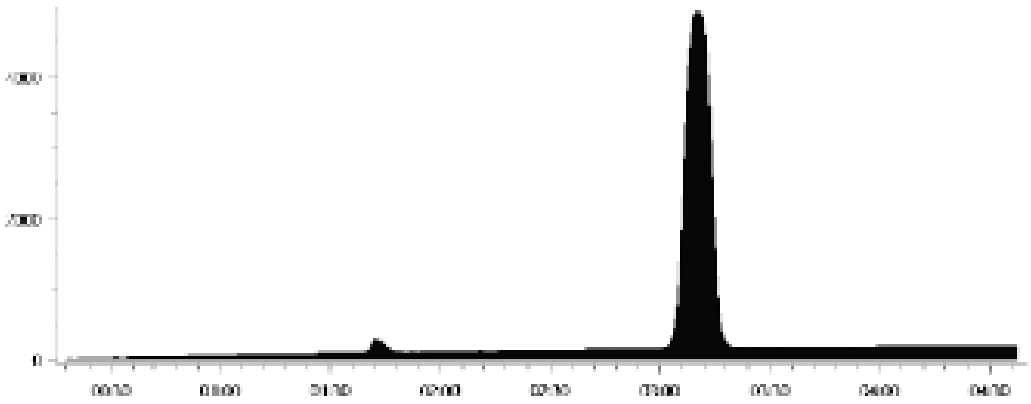
14h

#	Compound	Retention Time	Area	% Area	Height
1		03:14.0	22581.2	100.0	3724.79

miniLC

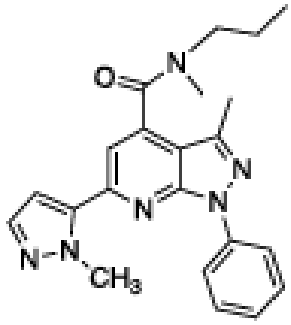
Method: 6 MINUTE ISOCRATIC 80% acn
Batch: JH
Sample: MSU-MLG-1-186
User: Administrator
S/N: 0118000000
Date: 11/18/2022 11:46 PM





14i

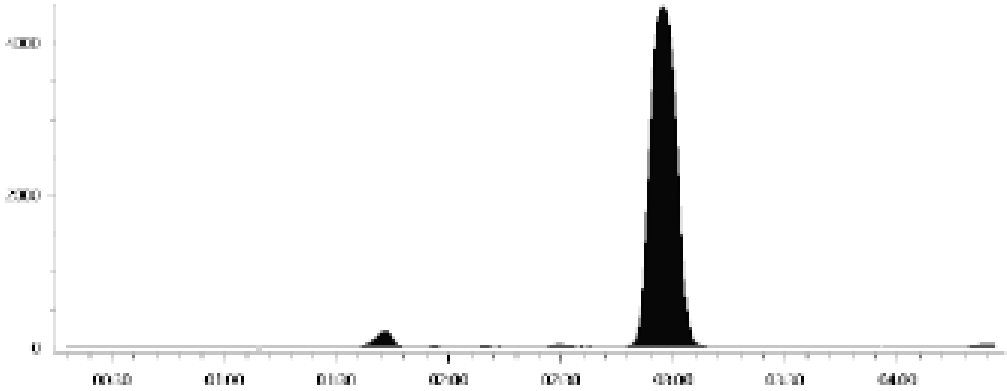
#	Compound	Retention Time	Area	% Area	Height
1		01:43.5	762.2	2.1	151.69
2		03:10.5	36349.9	97.9	4773.29



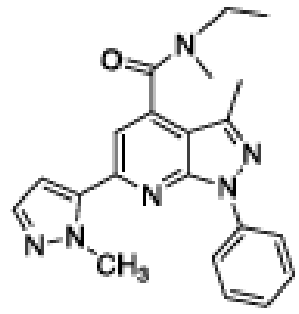
14j

miniLC

Method: 6 MINUTE ISOCRATIC 80% acn
Batch: MLG-SECOND
Sample: MSU-MLG-1-195
User: Administrator
S/N: 0118000000
Date: 11/17/2022 12:30 AM



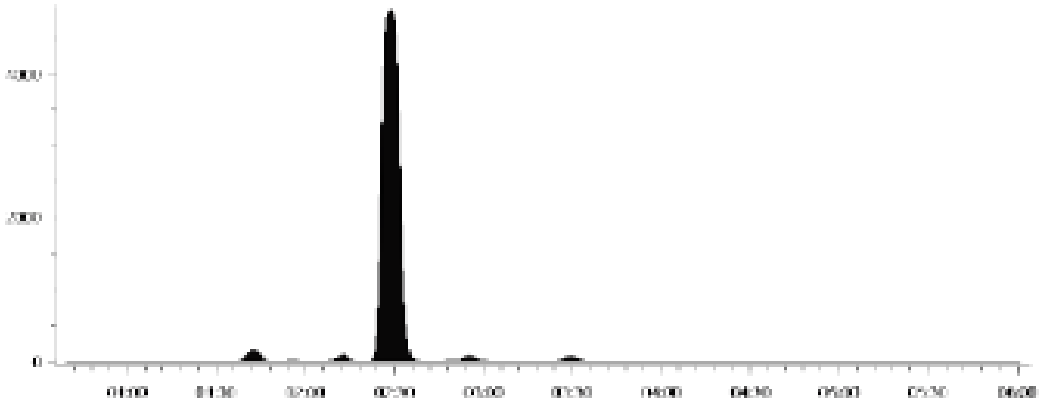
#	Compound	Retention Time	Area	% Area	Height
1		01.43.0	1083.7	2.9	200.37
2		02.57.5	35273.6	97.1	4460.43



14k

miniLC

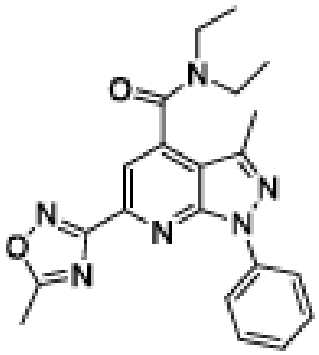
Method: 6 MINUTE ISOCRATIC 80% acn
Batch: LK
Sample: MSU-MLG-1-199
User: Guest
S/N: 0118000000
Date: 11/30/2022 4:54 AM

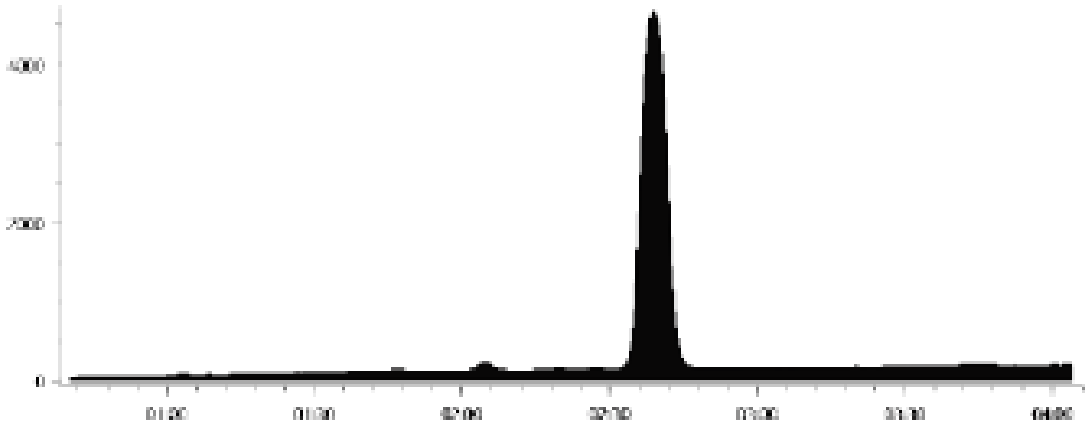


#	Compound	Retention Time	Area	% Area	Height
1		02.12.5	459.1	1.5	103.29
2		02.28.5	31401.4	95.9	4878.04
3		02.55.0	449.7	1.4	67.15
4		03.29.5	166.5	1.2	77.55

miniLC

Method: 6 MINUTE ISOCRATIC 80% acn
Batch: A
Sample: MSU-SMQ-1-067AA
User: Administrator
S/N: 01180000000
Date: 09/16/2022 1:41 AM



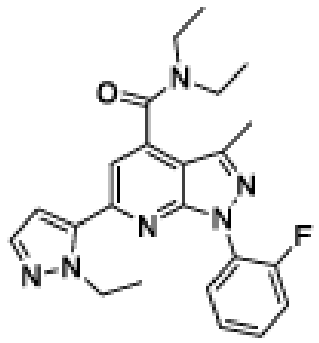


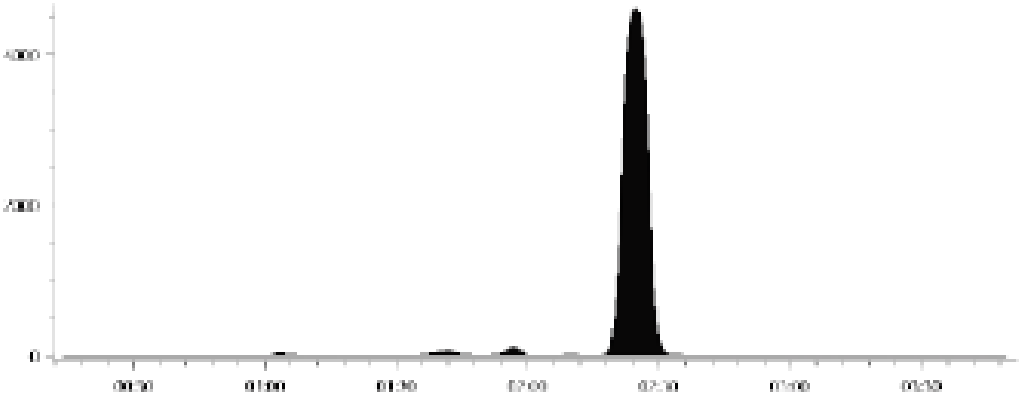
15

#	Compound	Retention Time	Area	% Area	Height
1		02:04.5	365.1	1.4	92.28
2		02:39.0	25196.2	98.6	4438.05

miniLC

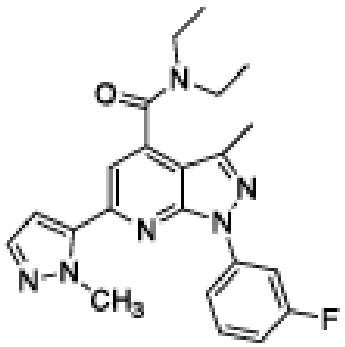
Method: 6 MINUTE ISOCRATIC 80% acn
Batch: ISOCRATIC ANALYSIS
Sample: MSU-SMQ-1-145AAA
User: Administrator
S/N: 01180000000
Date: 09/16/2022 1:23 AM





18a

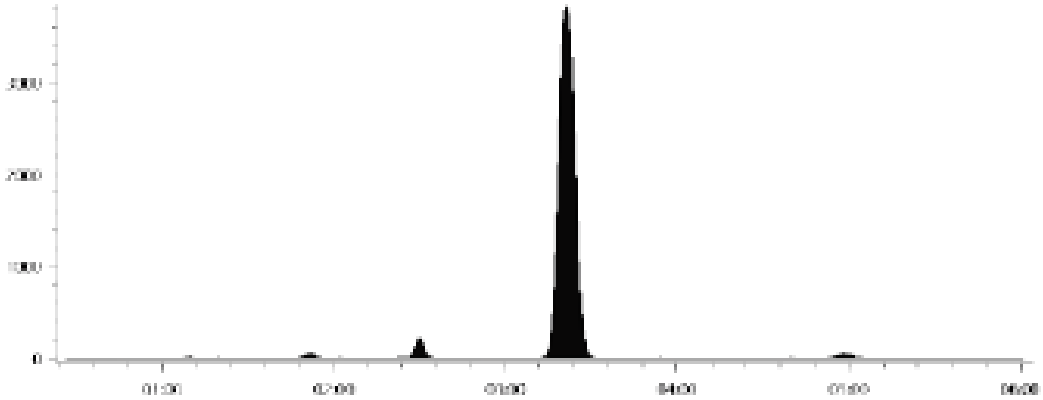
#	Compound	Retention Time	Area	% Area	Height
1		01:41.5	488.6	1.6	68.57
2		01:56.5	516.9	1.7	110.25
3		02:24.5	29796.3	96.7	4603.42



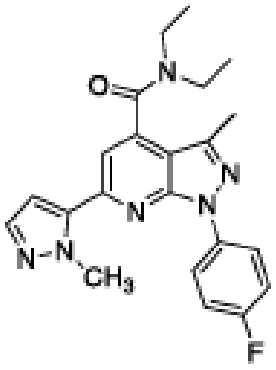
18b

miniLC

Method: 6 MINUTE ISOCRATIC 80% acn
Batch: UV
Sample: MSU-TSH-1-40
User: Guest
S/N: 01180800000
Date: 11/30/2022 12:23 AM



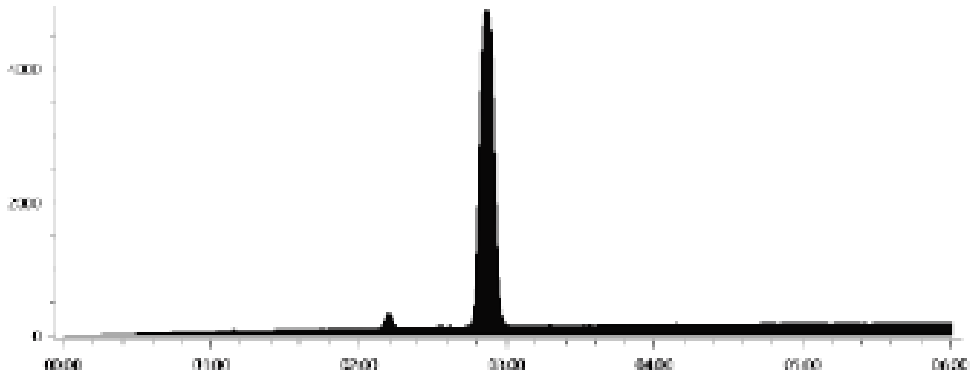
#	Compound	Retention Time	Area	% Area	Height
1		01.52.0	239.3	0.9	58.27
2		02.30.0	634.7	3.3	199.78
3		03.21.5	24328.1	94.3	3822.70
4		[illegible]	407.5	1.6	95.85



18c

miniLC

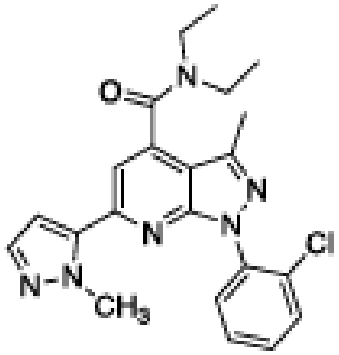
Method: 6 MINUTE ISOCRATIC 80% acn
Batch: NR
Sample: MSU-TSH-1-43
User: Administrator
S/N: 01180800000
Date: 11/29/2022 4:16 AM

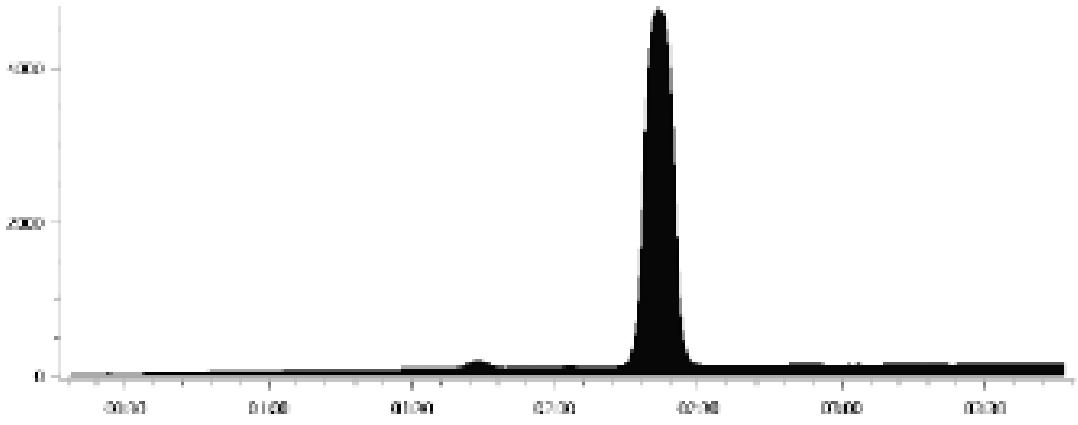


#	Compound	Retention Time	Area	% Area	Height
1		02.12.0	1642.4	2.3	274.16
2		02.52.0	33036.2	97.7	4736.27

miniLC

Method: 6 MINUTE ISOCRATIC 80% acn
Batch: J
Sample: MSU-SMG-1-160
User: Guest
S/N: 0118000000
Date: 11/11/2022 11:36 PM



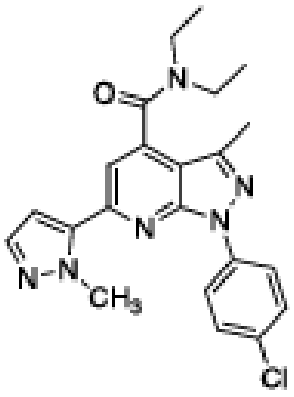


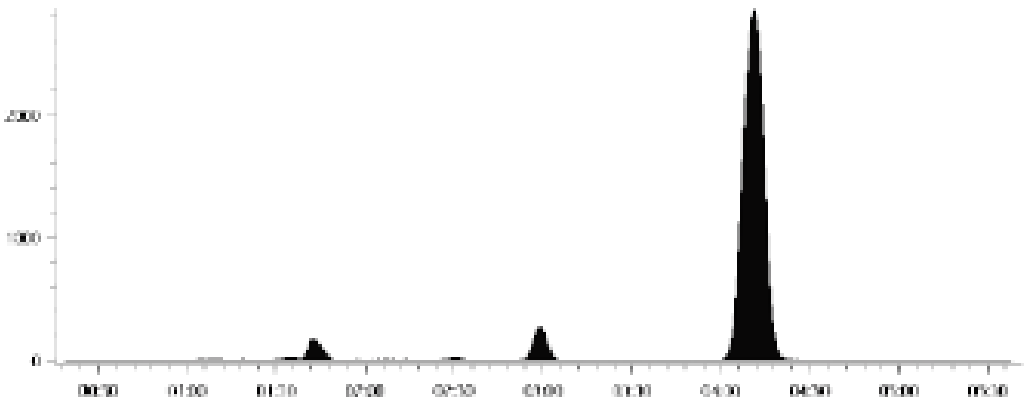
18d

#	Compound	Retention Time	Area	% Area	Height
1		01.44.0	438.7	1.4	98.47
2		02.21.5	30471.8	98.6	4627.16

miniLC

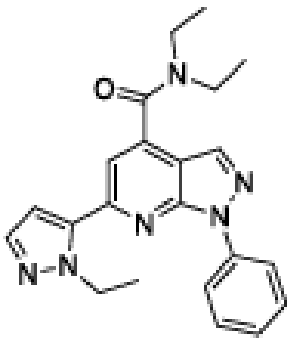
Method: 6 MINUTE ISOCRATIC 80% acn
Batch: kj
Sample: MSU-TSR-1-56
User: Guest
S/N: 0118000000
Date: 11/28/2022 11:36 PM





18e

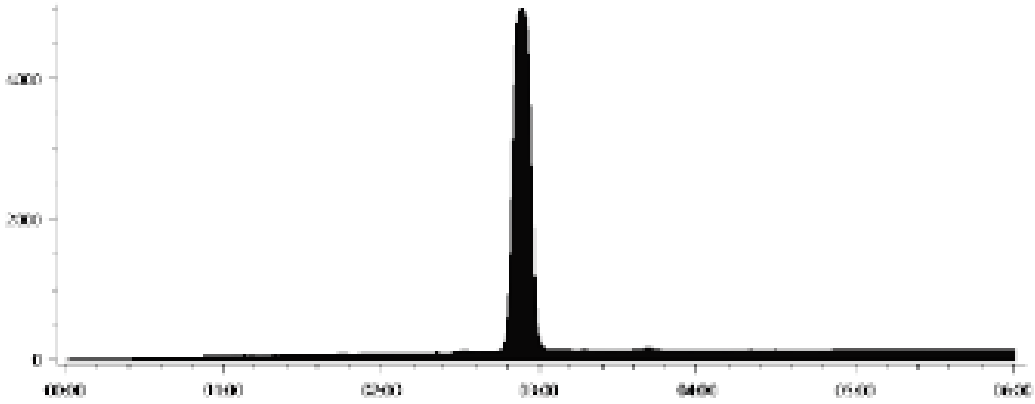
#	Compound	Retention Time	Area	% Area	Height
1		01.43.0	750.4	3.0	147.89
2		02.59.0	1385.0	5.6	265.61
3		04.11.0	22693.3	91.4	2844.40



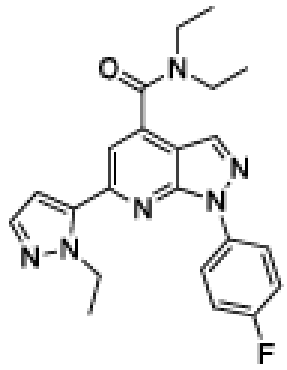
20a

miniLC

Method: 6 MINUTE ISOCRATIC 80% acn
Batch: M
Sample: MSU-SMQ-1-80
User: Guest
S/N: 0118000000
Date: 11/09/2022 1:07 AM



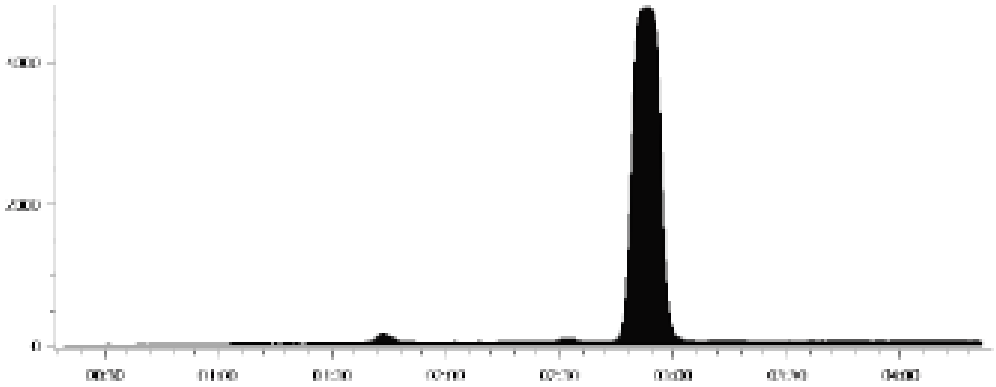
#	Compound	Retention Time	Area	% Area	Height
1		02:53.5	47378.6	100.0	4940.43



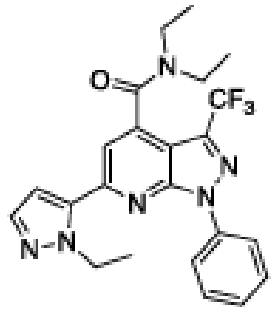
20b

miniLC

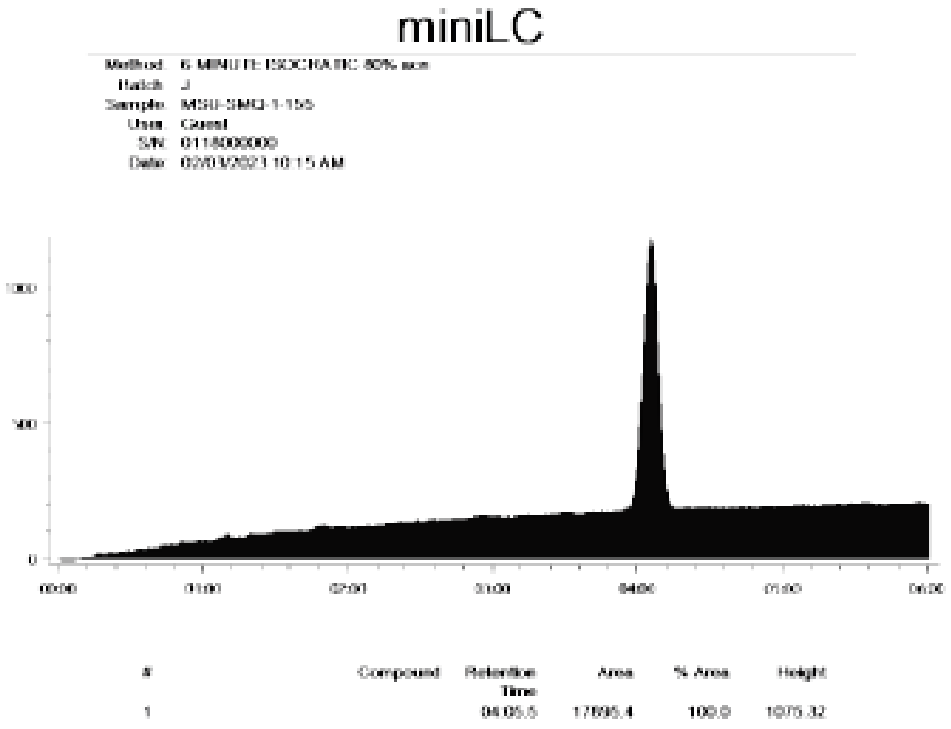
Method: 6 MINUTE ISOCRATIC 80% acn
Batch: M
Sample: MSU-SMQ-1-100
User: Guest
S/N: 0118000000
Date: 11/11/2022 11:06 PM



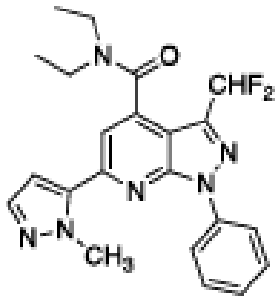
#	Compound	Retention Time	Area	% Area	Height
1		01:43.5	680.9	1.7	126.81
2		02:32.0	221.5	0.5	50.06
3		02:53.0	40318.1	97.8	4694.40



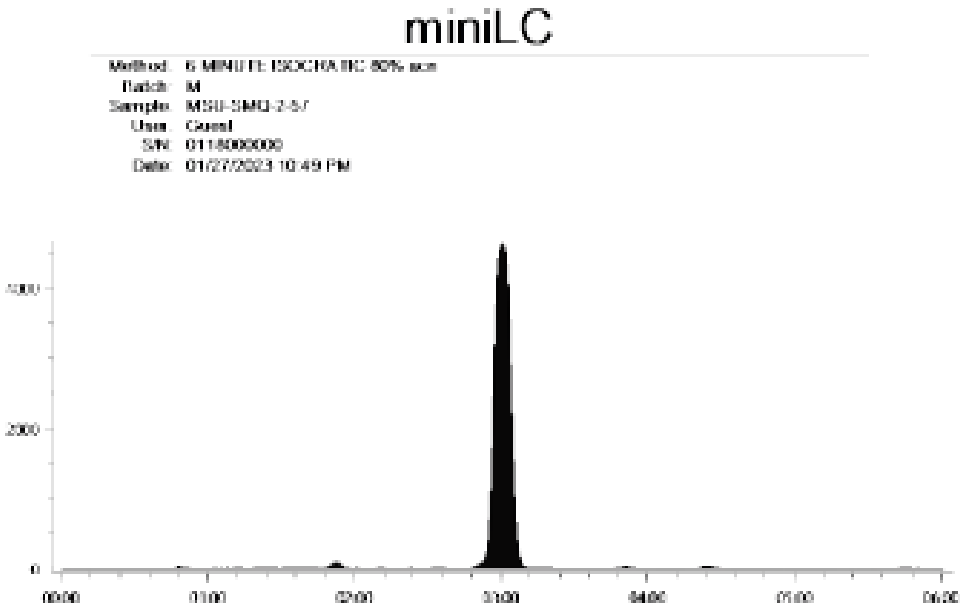
23a



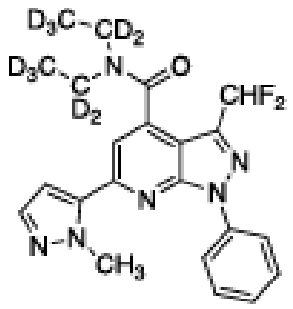
#	Compound	Retention Time	Area	% Area	Height
1		04:05.5	17695.4	100.0	1075.32



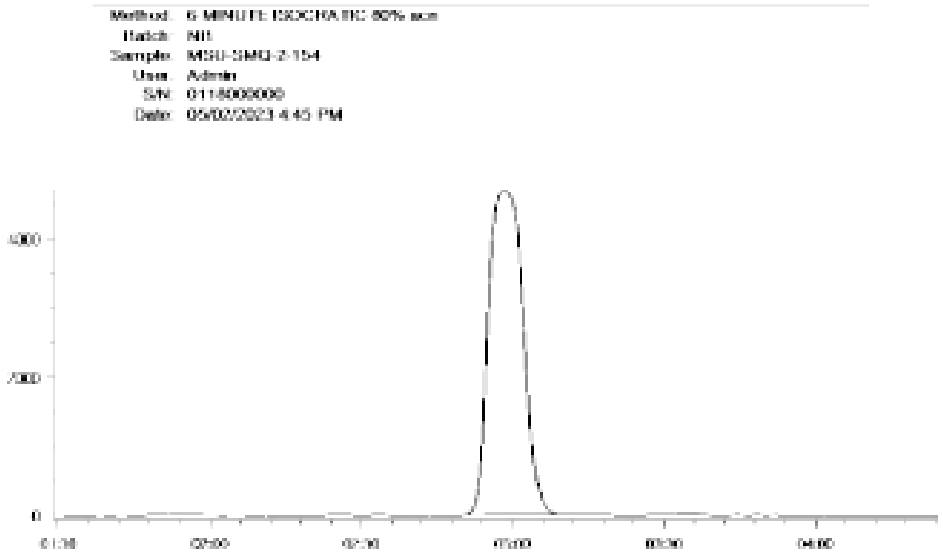
23b



#	Compound	Retention Time	Area	% Area	Height
1		01:52.5	1121.2	1.0	89.76
2		03:00.5	362754	99.0	4638.15



25



#	Compound	Retention Time	Area	% Area	Height
1		02:56.5	37954.3	100.0	4675.43

Mass spectrum of 25

==== Shimadzu LabSolutions Data Report ====

<Spectrum>

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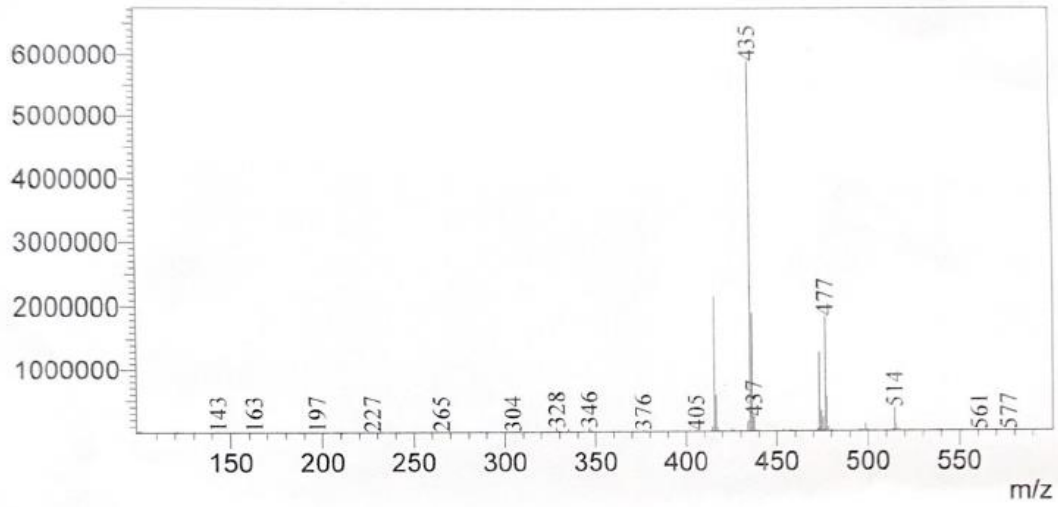
MassPeaks:500
RawMode:Single 11.817(710) BasePeak:435(5905113)
BG Mode:None Segment 1 - Event 1



Expanded PDE Selectivity Screening 14b & 23b

Table S-1 Inhibitory Effects of the Compounds on PDE Activities

Inhibitors	% Inhibition									
	PDE4A1A	PDE4B1	PDE4C1	PDE4D7	PDE7A1	PDE7B	PDE8A1	PDE9A2	PDE10A1	PDE10A2
SMQ-2-057 (**23b**), 1 μM	1	5	15	16	2	1	1	1	4	2
SMQ-2-057 (**23b**), 10 μM	24	14	34	33	2	51	11	2	10	3
SMQ-1-148 (**14b**), 1 μM	5	2	14	1	0	0	1	2	3	2
SMQ-1-148 (**14b**), 10 μM	8	4	36	5	8	3	7	1	5	6
Apremilast ~ 0.1 x IC_{50}	9	10	8	8	-	-	-	-	-	-
Apremilast ~ 1 x IC_{50}	50	54	41	53	-	-	-	-	-	-
Apremilast ~ 10 x IC_{50}	93	94	87	93	-	-	-	-	-	-
BRL-50481 ~ 0.1 x IC_{50}	-	-	-	-	9	-	-	-	-	-
BRL-50481 ~ 1 x IC_{50}	-	-	-	-	51	-	-	-	-	-
BRL-50481 ~ 10 x IC_{50}	-	-	-	-	93	-	-	-	-	-
Dipyridamole ~ 0.1 x IC_{50}	-	-	-	-	-	10	10	-	-	-
Dipyridamole ~ 1 x IC_{50}	-	-	-	-	-	48	50	-	-	-
Dipyridamole ~ 10 x IC_{50}	-	-	-	-	-	86	89	-	-	-
Bay 73-6691 ~ 0.1 x IC_{50}	-	-	-	-	-	-	-	8	-	-
Bay 73-6691 ~ 1 x IC_{50}	-	-	-	-	-	-	-	52	-	-
Bay 73-6691 ~ 10 x IC_{50}	-	-	-	-	-	-	-	90	-	-
Papaverine ~ 0.1 x IC_{50}	-	-	-	-	-	-	-	-	11	9
Papaverine ~ 1 x IC_{50}	-	-	-	-	-	-	-	-	54	51
Papaverine ~ 10 x IC_{50}	-	-	-	-	-	-	-	-	91	95

Table S-2. PDE11A4 protein expression (normalized by Ponceau staining and expressed as a fold-change of DMSO) measured in drug-treated transiently-transfected HT-22 cell samples used in the PDE assay confirms that the decrease in PDE11A4 catalytic activity caused by these compounds is not explained by a reduction in expression of the protein itself.

	1	**14b**	**25**
DMSO	1.0±0	1.0±0.14	1±0
0.1 μM	1.32±0.27	1.02±0.10	1.16±0.12
1 μM	1.21±0.29	1.10±0.07	1.04±0.17
10 μM	1.12±0.17	0.819±0.14	1.25±0.19
100 μM	0.94±0.03	0.78±0.10	1.19±0.12

Neither 1 (failed normality; ANOVA on Ranks: H(4)=1.04, P=0.4), 14b (F(4,15)=1.46, P=0.263) nor 25b (F(4,15)=0.56, P=0.697) significantly changed PDE11A4 protein expression. Data expressed as mean ±SEM.

Table S-3. The number of intact transiently transfected cells counted in a separate study of drug-treated HT-22 cells confirms that the decrease in PDE11A4 catalytic activity caused by these compounds is not explained by a loss of PDE11A4-expressing cells.

	1	**14b**	**25**
DMSO	100±21.9	63.8±4.6	73±5
0.1 μM	92±6.2	51.2±4.3	77.5±7.2
1 μM	86.5±12.7	53±3.7	92±7.3
10 μM	88.3±12.3	61.8±4.0	78.5±9.1
100 μM	76.84±10.1	61.5±2.7	71.5±2.4

Sample images for quanitification were taken using an inverted Leica microscope with a 10x objective. All cells within the field of view showing expression of the GFP-PDE11A4 recombinant protein were counted by an experimenter blind to treatment. Neither 1 ($F(4,15)=0.38$, $P=0.817$), 14b ($F(5,18)=2.09$, $P=0.132$) nor 25b ($F(4,15)=1.50$, $P=0.251$) significantly changed the total number of cells expressing PDE11A4 protein. Data expressed as mean ±SEM.