Parallel Synthesis of Piperazine Tethered Thiazole Compounds with Antiplasmodial Activity

Ramanjaneyulu Rayala [1], Prakash Chaudhari [1], Ashley Bunnell [1],

Bracken Roberts[2], Debopam Chakrabarti[2], and Adel Nefzi [1]*

[1] Herbert Wertheim College of Medicine, Center for Translational Science, Florida International University

[2] Division of Molecular Microbiology, Burnett School of Biomedical Sciences, University of Central Florida, Orlando, FL 32826, USA

Supporting Information

Table of Contents:

Materials and General Methods:

Reagents and solvents were purchased from various commercial sources (Sigma Aldrich, Chemimpex, VWR, Cambridge Isotopes, etc.) and used without further purification unless otherwise stated. Yields were based on the manufacturer's reported loading of MBHA resin of 1.15 mmole per gram of resin. ^{1}H NMR spectra were recorded at 400 MHz and ^{13}C NMR were recorded at 100 MHz in deuterated chloroform and all chemical shifts are reported in δ units relative to TMS. All L-amino acids used were assumed to be enantiomerically pure from the supplier. LC-MS was performed on crude samples dissolved in 50:50 (acetonitrile and water) at a concentration of 1 mg/ mL on a Shimadzu LC-MS equipped with a Vydac column with a gradient of 5 – 95 % formic acid in acetonitrile over 7 minutes with their UV traces monitored at λ = 214 and 254 nm. HPLC purification was performed on a Phenomenex Luna 150 x 21.2 mm 5 micron column with a flow rate of 12 mL/min.

Synthesis of compounds 2291:

- **Bag preparation and resin functionalization**

A 100-mg sample of p-methylbenzhydrylamine hydrochloride (MBHA ·HCl) resin (CHEM-IMPEX INTERNATIONAL) with a molar loading of 1.15 mmole/g and size of 100 -200 mesh, was thermally sealed into a polypropylene mesh bag. All bags were made in the same fashion. The bags were washed in triplicate with dichloromethane, 5 % diisopropylethylamine in dichloromethane, and finally dichloromethane to neutralize the acidic resin. The neutralized resin bags were then treated with 3 equivalents of Boc-Phe(4-NO_2)-OH (3.2 grams), HOBt (1.6 grams) and DIC (2.1 mL) in 75 mL of DMF in a 150-mL polystyrene bottle. The bottle was placed on a mechanical shaker and left for approximately 15 hours. A ninhydrin test was used on a few grains of the resin to confirm the complete acylation of the resin amine.

- **Boc Deprotection**

The Boc protecting group was routinely removed from the N-terminus by shaking the tea bags in a 55 % solution of trifluoroacetic acid in dichloromethane for 30 minutes. Upon completion of the TFA treatment, the bags were thoroughly washed with dichloromethane (x3), neutralized with 5 % DIEA in dichloromethane (x 4) and washed with DCM (x3). Upon addition of the DIEA, the resin within the tea bags typically changes from a red/ orange color to a yellow/ white color.

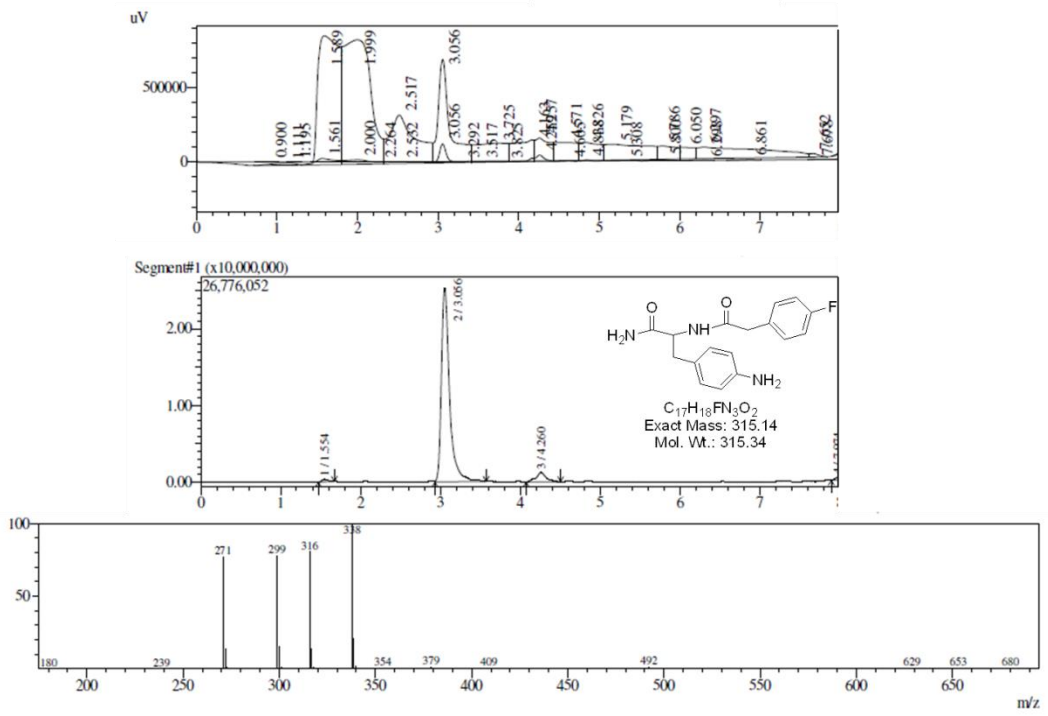
- **N-Terminus Acylation**

The N-terminus was acylated using different carboxylic acids. All acylations were carried out with 10 equivalents of the acid, and 10 equivalents of DIC in DMF. The reactions were allowed to shake overnight (~15 hours) before they were thoroughly washed with DMF followed by DCM. A ninhydrin test of a few grains of resin confirmed that all of the acylations were complete.

- **Stannous Chloride Reduction**

All bags were combined into a 150-mL polystyrene bottle. Stannous chloride (20 eq, 13.1 grams) was added to the bottle along with 69 mL of DMF to afford a concentration of 1.0 M. The bottle was gently sonicated for approximately 20 minutes to ensure a homogenous solution and then set

to shaking overnight (~15 hours). In the morning the bags were washed 12 times with DMF, 6 times with MeOH and 6 times with DCM to ensure complete removal of the tin. A few milligrams of resin were then removed from the bag acylated with 4-Fluoropheyl acetic acid and used as a control to confirm complete reduction by cleavage in HF for 1.5 hours. LC-MS of the resulting product confirmed the reduction was complete.



- **Installation of Fmoc Protected thio-amide**

All bags were combined in a 150-mL polystyrene bottle. Fmoc-NCS (2.5 equivalents) was weighed out quickly and added to the polystyrene bottle. The bottle was purged with nitrogen gas for approximately 10 minutes before anhydrous DMF (~ 60 mL) was added via canula. The bottle was covered and sealed with parafilm and then sonicated for ~10 minutes to ensure a homogenous solution. The bottle was shaken on a mechanical shaker overnight. In the morning, the bags were thoroughly washed with DMF and DCM.

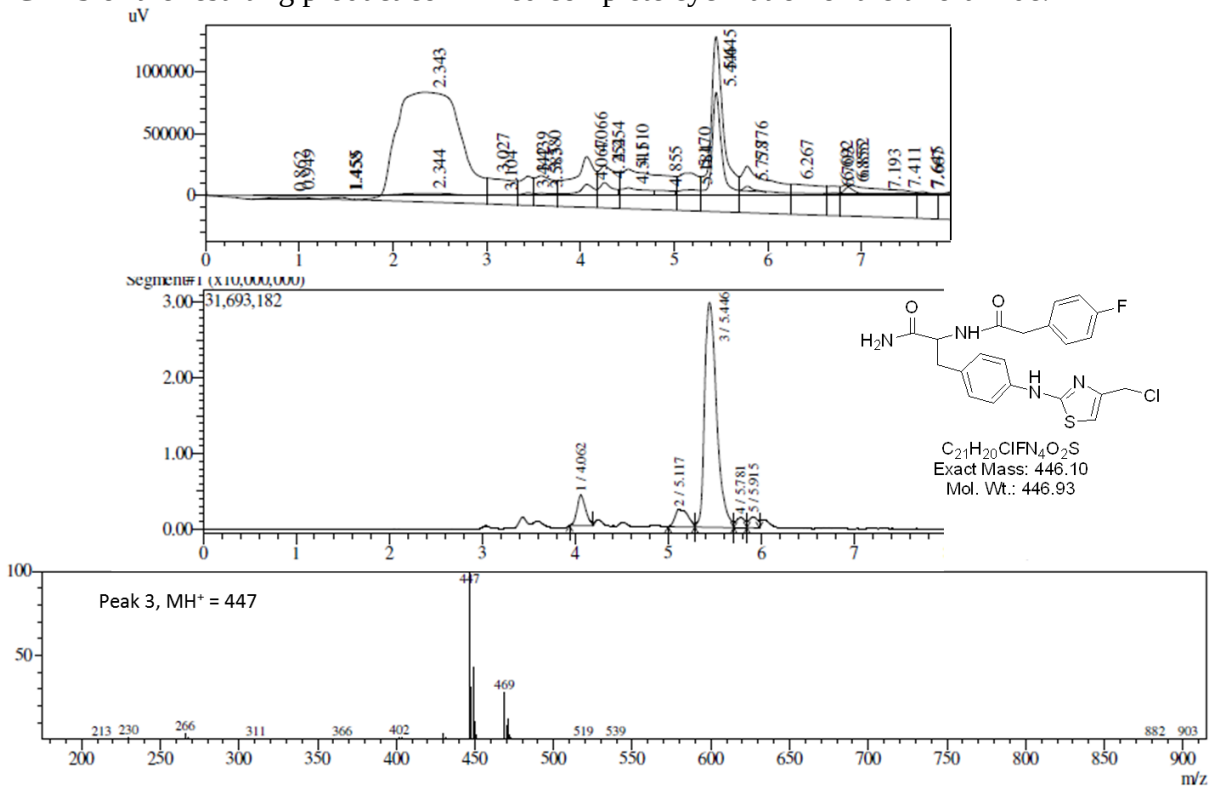
- **Fmoc Cleavage**

All bags were combined in a 150-mL polystyrene bottle. The bottle was then filled half way with a 20 % solution of piperidine in DMF. The bottle was allowed to shake for 10 minutes at room temperature before the solution was poured off and the procedure repeated. The bags were then thoroughly washed with DMF and DCM to ensure complete removal of the piperidine.

- **Hantzch's Cyclization**

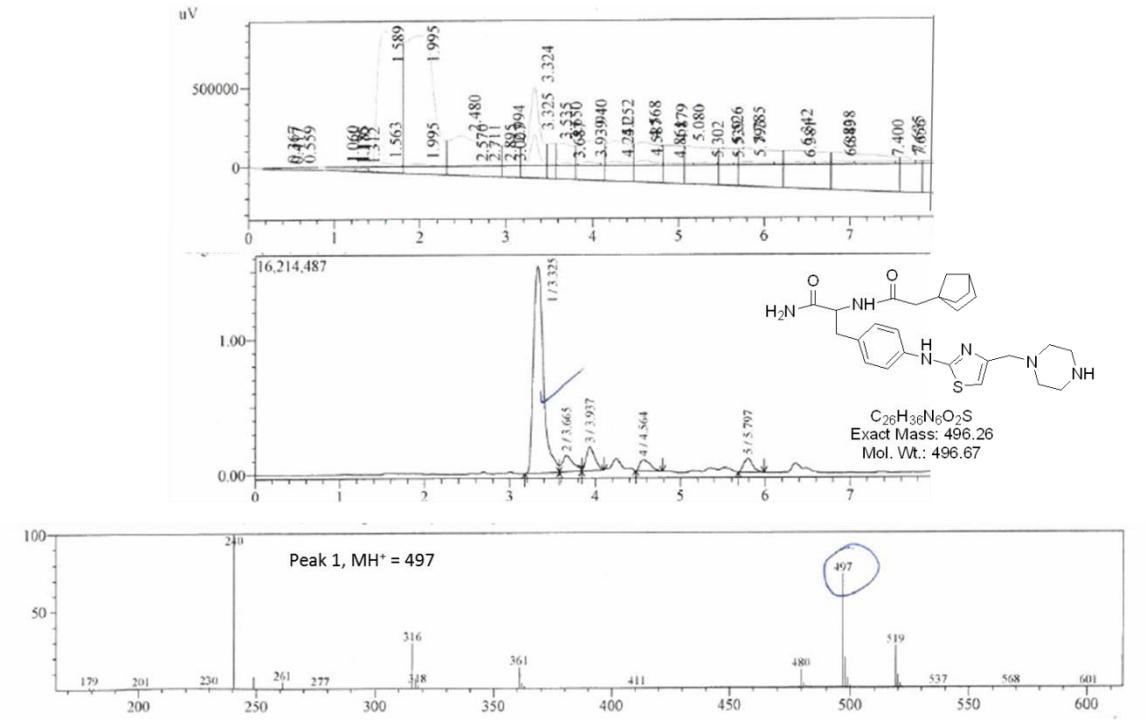
All 30 bags were sealed into a mesh bag and then added to a reflux glassware equipped with a condensing column and heating mantle. The system was purged with nitrogen for 10 minutes before 10 equivalents of 1,3-dichloroacetone was added. 115 mL of anhydrous DMF was added via canula with all bags submerged below the solvent. An internal thermometer was added and the

cyclization was carried out at 85 ^{o}C overnight. In the morning the colorless solution had turned a dark brown color, which is indicative of this reaction. The bags were thoroughly washed with DMF and DCM and placed on the under vacuum at 0^{o} C until they were used in the next step. A few milligrams of the same bag was again used as a control and cleaved for 1.5 hours in HF. The LC-MS of the resulting product confirmed complete cyclization of the thio-amide.



- **Boc-Piperazine Displacement of Chloride**

All bags were added to a 150-mL polystyrene bottle. Boc-piperazine (6 equivalents) was added to the bottle along with 100 mL of DMF. Diisopropylethylamine (6 equivalents, 3.61 mL) was added lastly and the bottle was closed and allowed to shake at room temperature overnight. In the morning, the bags were washed with DMF and DCM. A few milligrams of bag #24 were removed from the main bag, treated with TFA to remove the Boc protecting group and cleaved as a control in HF for 1.5 hours. The LC-MS of the resulting product confirmed complete nucleophilic displacement of the chloride.



- **Boc Protecting Group Cleavage**

The Boc protecting group was removed from the piperazine by shaking the tea bags in a 55 % solution of trifluoroacetic acid in dichloromethane for 30 minutes, twice. Upon completion of the second TFA treatment, the bags were thoroughly washed with dichloromethane (x3), neutralized with 5 % DIPEA (x 4) in dichloromethane and washed with DCM (x3). Upon addition of the DIPEA, the resin within the teabags typically changes from a red/ orange color to a yellow/ white color.

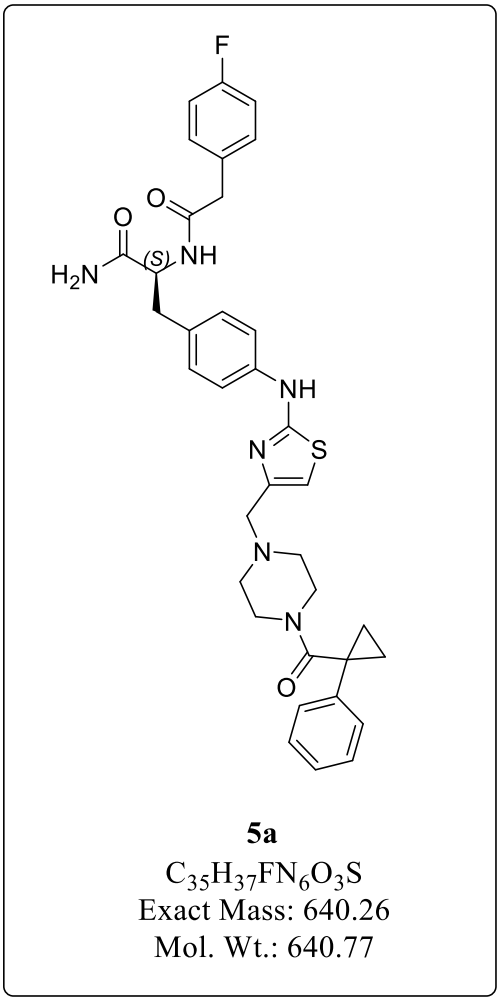
- **Piperazine Acylation**

The piperazine was acylated using different carboxylic acids such that bags. All acylations were carried out with 10 equivalents of the acid, and 10 equivalents of DIC in 25 mL of THF. The reactions were allowed to shake overnight (~15 hours) before they were thoroughly washed with DMF followed by DCM.

- **Cleavage from the Solid Support**

The dried bags were treated with hydrofluoric acid at 0 ^{o}C for 1.5 hours before the HF was blown-off with nitrogen. The bags were then extracted for 1 hour in 5 mL of 95 % acetic acid. The extraction was repeated twice. The acetic acid extracts were then transferred to glass scintillation flasks, frozen and lyophilized. The crude samples were taken up in 6 – 8 mL of 50:50 acetonitrile and water and a sample was submitted for LC-MS analysis as a 1 mg/ mL sample. The crude samples were frozen and lyophilized again. This procedure was repeated for a total of three times. Upon completion of the third round, the crude samples were transferred to tared glass scintillation vials, frozen and lyophilized a final time. The final crude yields were obtained by subtracting the mass of the empty vial from the mass of the filled vial.

Product Characterization (5)



5a

$C_{35}H_{37}FN_6O_3S$

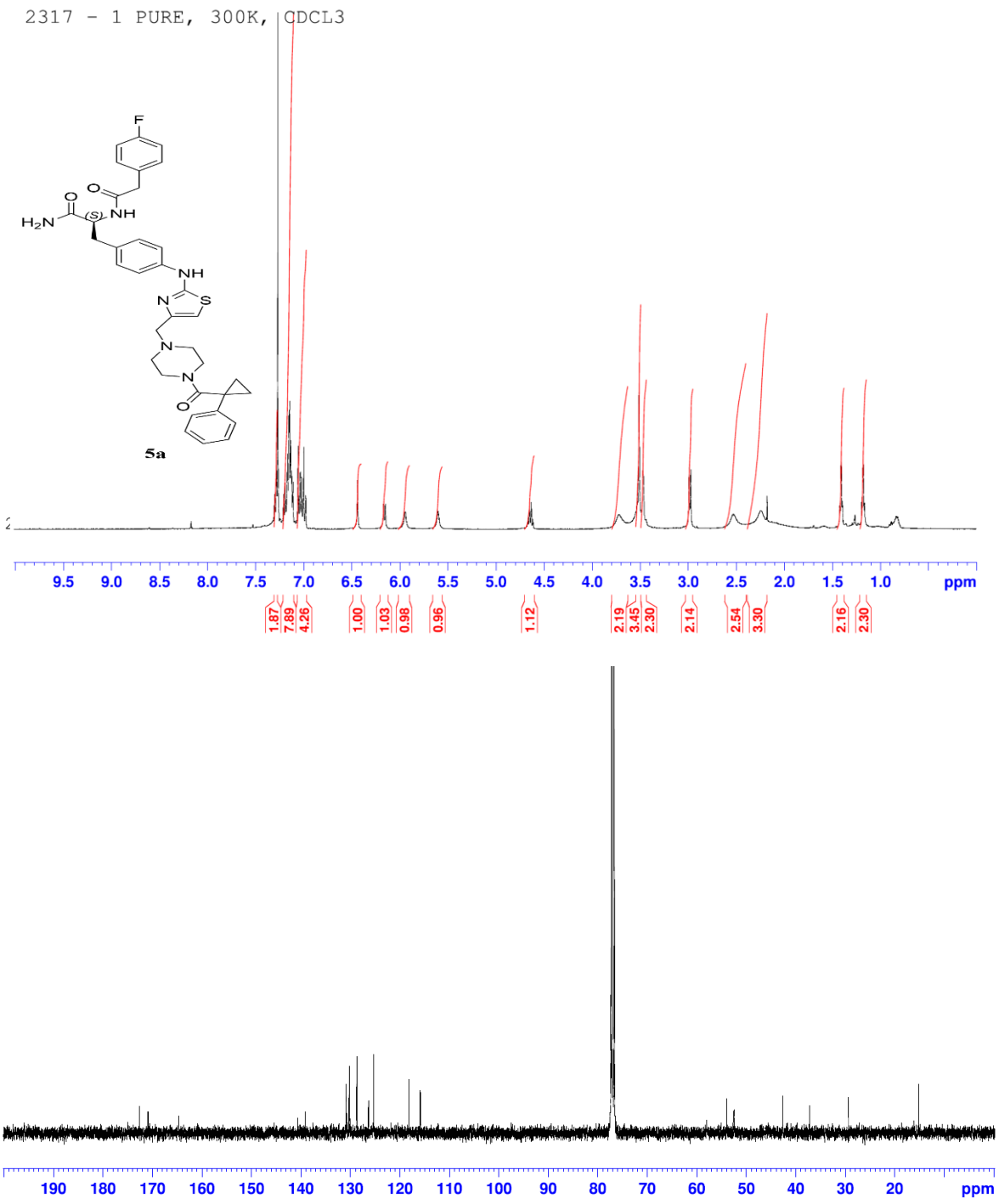
Exact Mass: 640.26

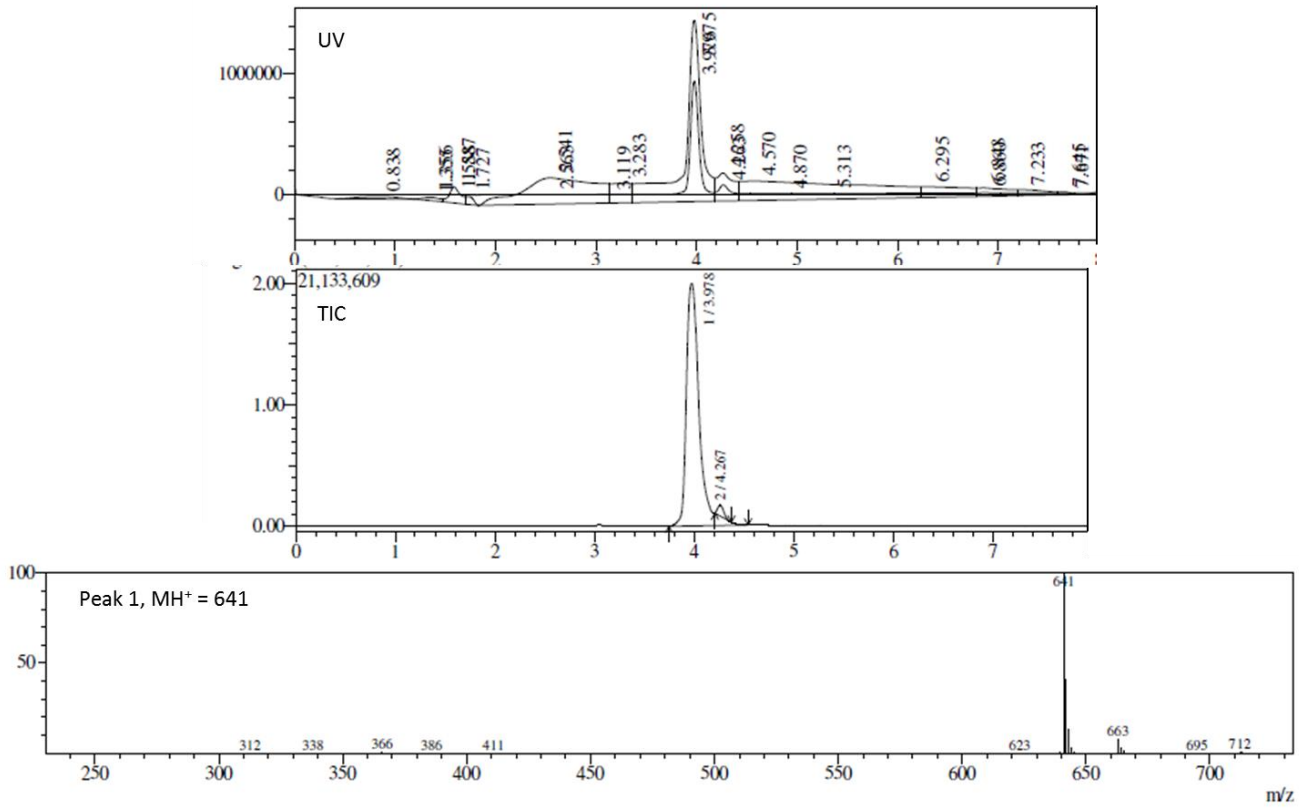
Mol. Wt.: 640.77

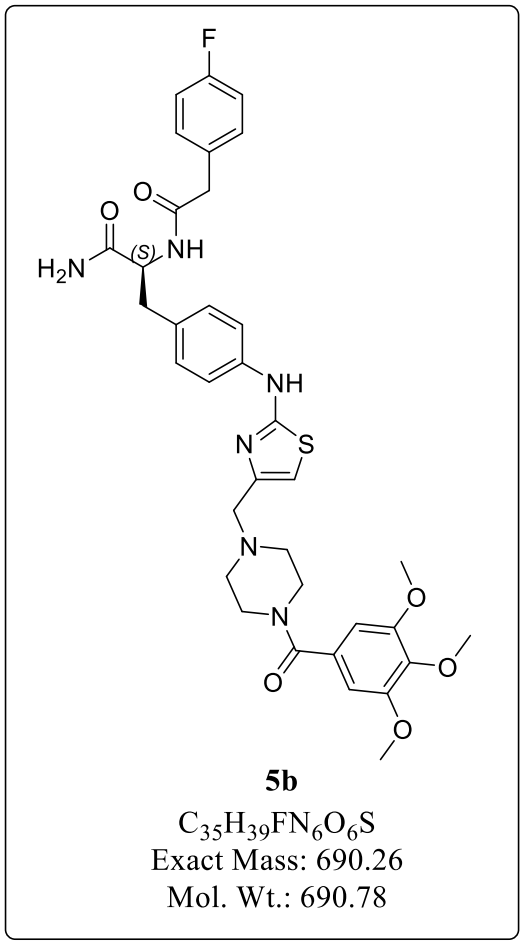
5a (^{1}H NMR, 400 MHz, $CDCl_3$, 300 K) δ 7.30 – 7.27 (m, 2H), 7.21 – 7.11 (m, 7H), 7.07 – 6.98 (m, 4H), 6.44 (s, 1H), 6.16 (d, J = 10.0 Hz, 1H), 5.94 ($s_{(broad)}$, 1H), 5.61 ($s_{(broad)}$, 1H), 4.64 (q, J = 9.3 Hz, 1H), 3.76 ($s_{(broad)}$, 2H), 3.51 (s, 2H), 2.17 (s, 2H), 2.98 (d, J = 8.6 Hz, 2H), 2.54 ($s_{(broad)}$, 2H), 2.24 ($s_{(broad)}$, 2H), 1.42 (m, 2H), 1.18 (m, 2H)

5a (^{13}C NMR, 100 MHz, $CDCl_3$, 300 K) δ 172.6, 171.0, 170.8, 164.7, 140.6, 139.2, 130.9, 130.8, 130.7. 130.2, 128.7, 126.4, 125.3, 118.2, 116.0, 115.8, 77.2, 58.8, 53.9, 52.5, 42.6, 37.2, 29.3, 15.1

LCMS: $C_{35}H_{37}FN_6O_3S$ (M calculated) 640.77, $C_{35}H_{38}FN_6O_3S$ (MH^+ found) 641


2317 - 1 PURE, 300K, CDCL3
F
O
NH
(S)
H2N
O
NH
N
S
N
N
O
5a
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.87 7.89 4.26 1.00 1.03 0.98 0.96 1.12 2.19 3.45 2.30 2.14 2.54 3.30 2.16 2.30
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm


UV
1000000
0
0.838
1.727
3.119
3.283
4.570
4.870
5.313
6.295
7.233
TIC
2.00
1.00
0.00
21,133,609
3.978
4.267
Peak 1, MH+ = 641
100
50
641
312
338
366
386
411
623
663
695
712
250
300
350
400
450
500
550
600
650
700
m/z



5b

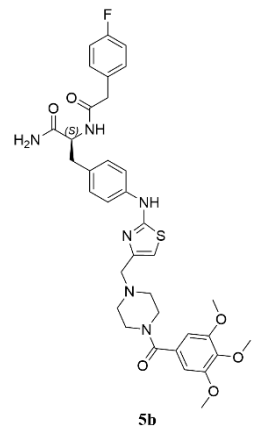
$C_{35}H_{39}FN_6O_6S$
Exact Mass: 690.26
Mol. Wt.: 690.78

5b (^{1}H NMR, 400 MHz, $CDCl_3$, 300 K) δ 7.18 (d, J = 13.3 Hz, 2H), 7.14 (t, J = 3.7 Hz, 2H), 7.06 (d, J = 8.8 Hz, 2H), 7.01 (t, J = 7.4 Hz, 2H), 6.64 (s, 2H), 6.55 ($s_{(broad)}$, 1H), 6.22 (d, J = 8.1 Hz, 1H), 6.03 ($s_{(broad)}$, 1H), 5.66 ($s_{(broad)}$, 1H), 4.66 (q, J = 9.3 Hz, 1H), 3.87 (s, 12H), 3.63 (s, 2H), 3.53 (s, 2H), 3.00 (d J = 8.1 Hz, 2H), 2.65 ($s_{(broad)}$, 4H)

5b (^{13}C NMR, 100 MHz, $CDCl_3$, 300 K) 1 δ 72.7, 170.8, 170.1, 164.7, 160.9, 158.8, 153.4, 139.1, 130.9, 130.8, 130.3, 118.2, 116.0, 115.7, 104.6, 77.2, 60.9, 56.3, 53.9, 42.6, 37.2

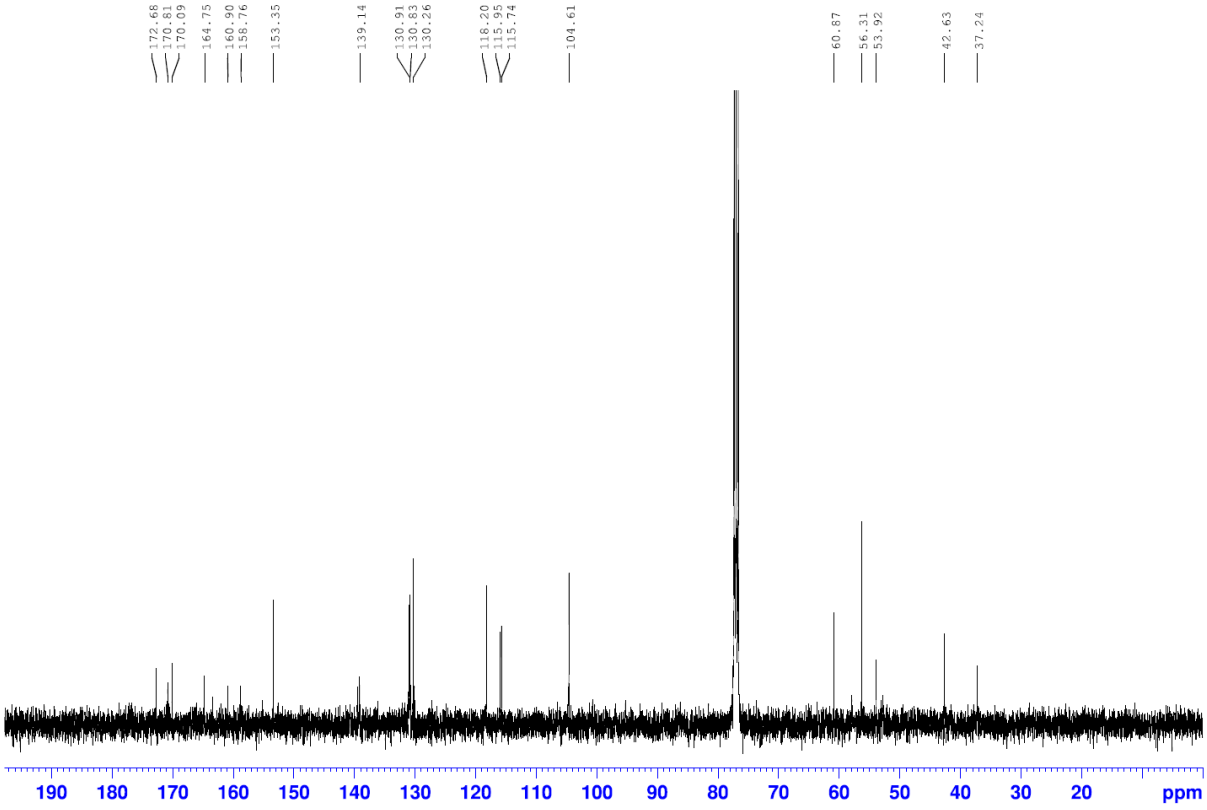
LCMS: $C_{35}H_{39}FN_6O_6S$ (M calculated) 690.78, $C_{35}H_{40}FN_6O_6S$ (MH^+ found) 691

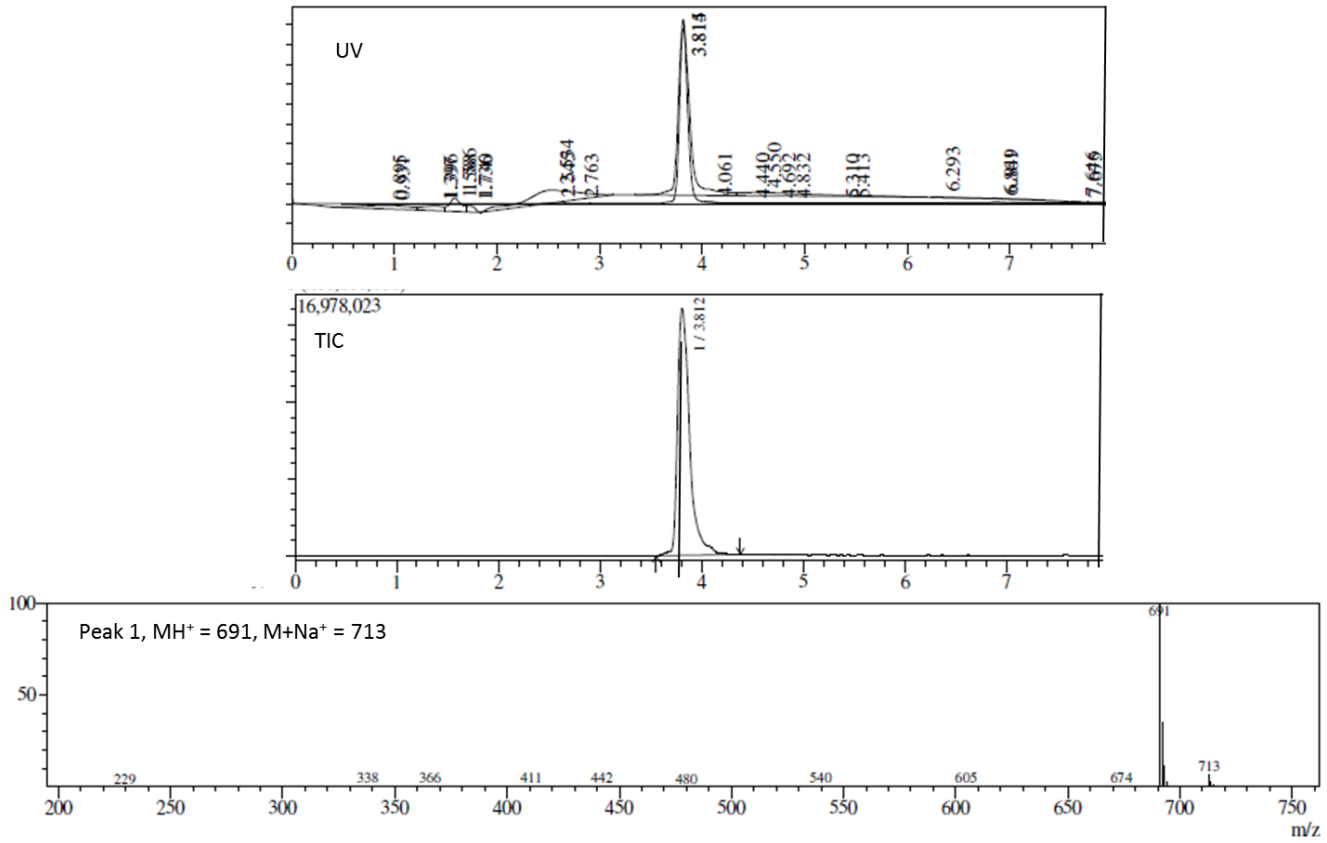
2317 - 3 PURE, 300K, CDCL3

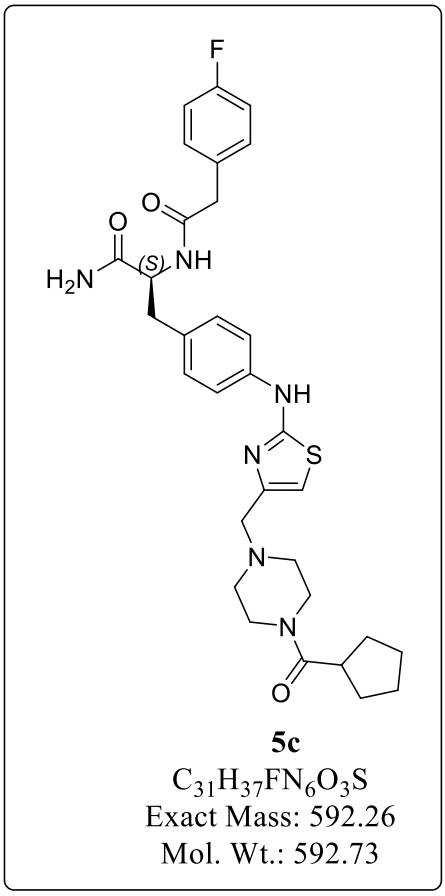


5b

317 - 3 PURE, 300K, CDCL3




UV
3.815
4.061
4.440
4.550
4.692
4.832
6.293
2.763
16,978,023
TIC
1 / 3.812
Peak 1, MH+ = 691, M+Na+ = 713
691
713
229
338
366
411
442
480
540
605
674
m/z



5c

$C_{31}H_{37}FN_6O_3S$

Exact Mass: 592.26

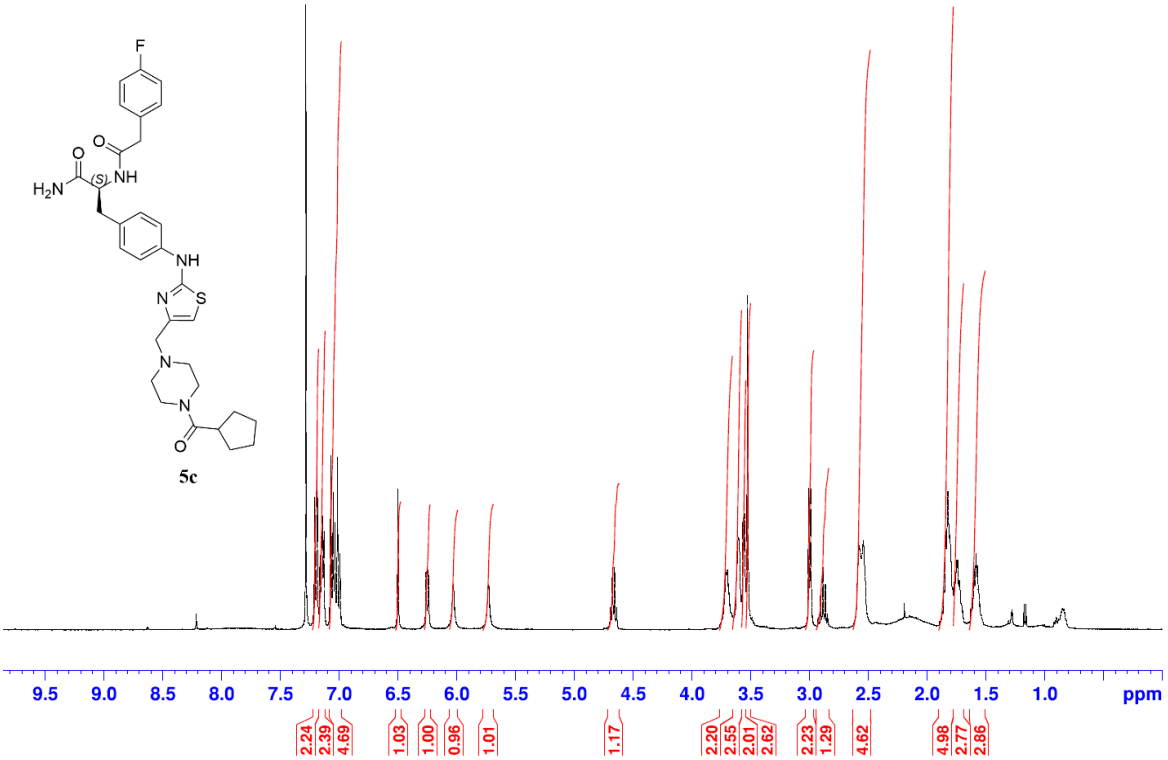
Mol. Wt.: 592.73

5c (¹H NMR, 400 MHz, $CDCl_3$, 300 K) δ 7.20 (d, J = 7.4 Hz, 2H), 7.15 (t, J = 8.2 Hz, 2H), 7.05 (d, J = 8.2 Hz, 2H), 7.00 (t, J = 8.9 Hz, 2H), 6.50 (s, 1H), 6.25 (d, J = 8.2 Hz, 1H), 6.03 ($s_{(broad)}$, 1H), 5.73 ($s_{(broad)}$, 1H), 4.66 (q, J = 7.4 Hz, 1H), 3.71 – 3.68 (m, 2H), 3.67 – 3.58 (m, 2H), 3.56 (d, J = 7.0 Hz, 2H), 3.53 (s, 3H), 3.00 (d, J = 7.8 Hz, 2H), 2.89 (pent. J = 7.0 Hz, 1H), 2.58 – 2.52 (m, 5H), 1.88 – 1.64 (m, 8H), 1.62 – 1.51 (m, 3H)

5c (¹³C NMR, 100 MHz, $CDCl_3$, 300 K) δ 174.5, 172.7, 170.8, 164.7, 163.4, 139.2, 130.9, 130.8, 130.6, 130.2, 118.2, 115.9, 115.7, 77.2, 58.2, 53.9, 42.6, 41.0, 37.2, 30.1, 26.0

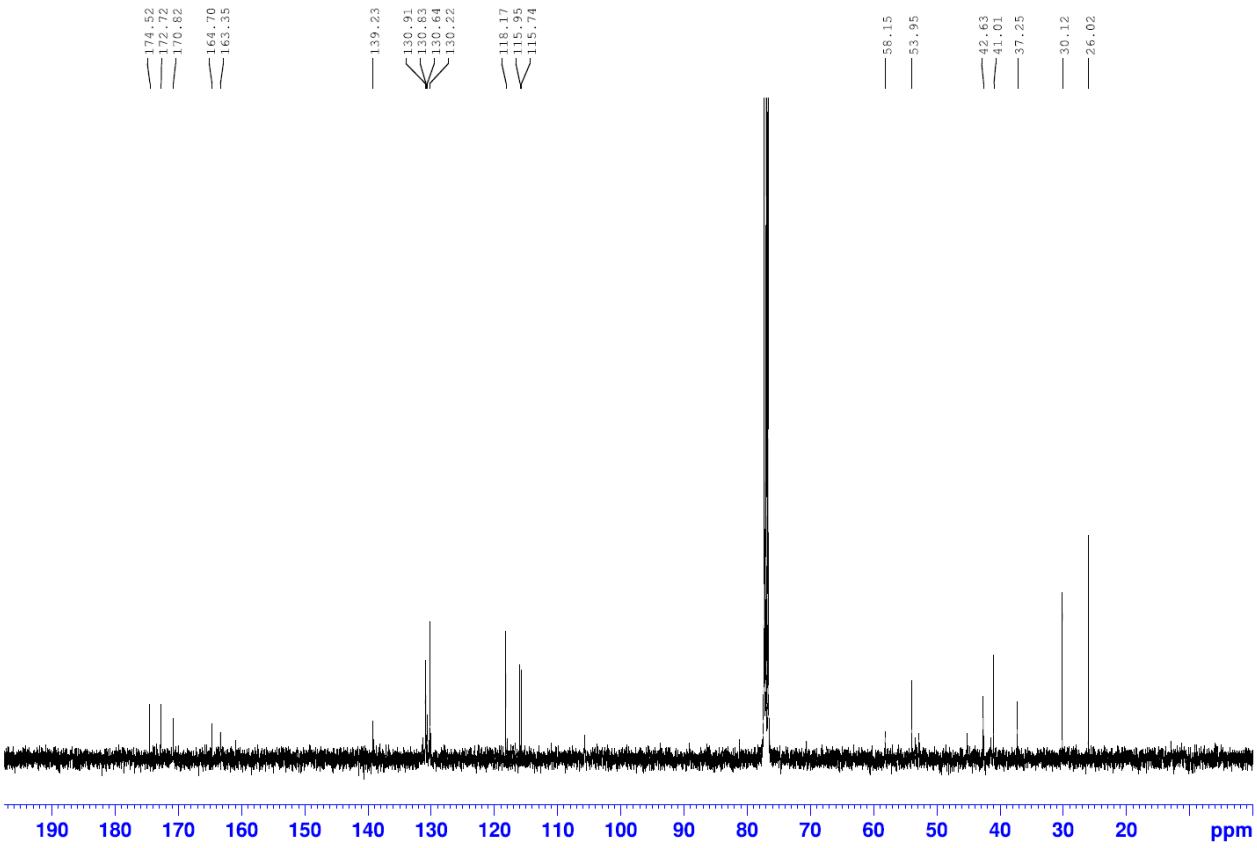
LCMS: $C_{31}H_{37}FN_6O_3S$ (M calculated) 592.73, $C_{31}H_{38}FN_6O_3S$ (MH^+ found) 593

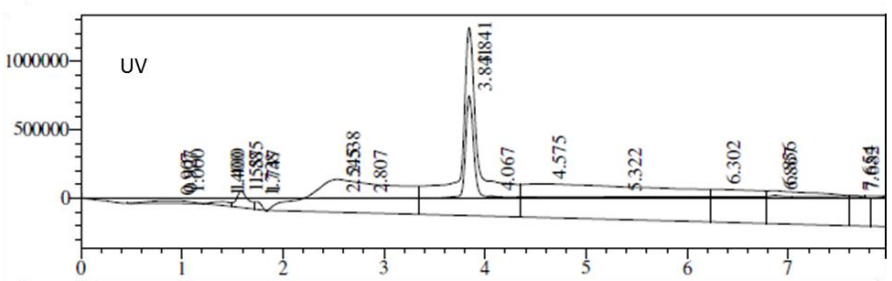
317 - 4 PURE, 300K, CDCL3

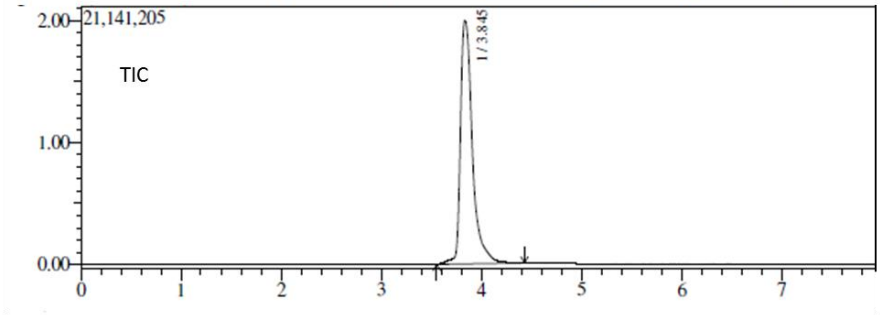


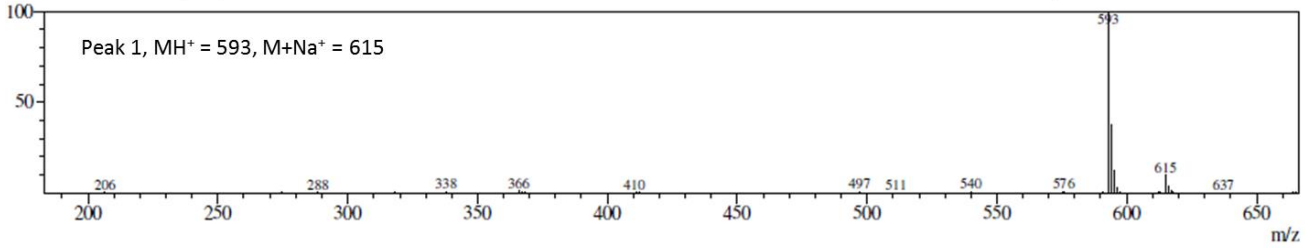
5c

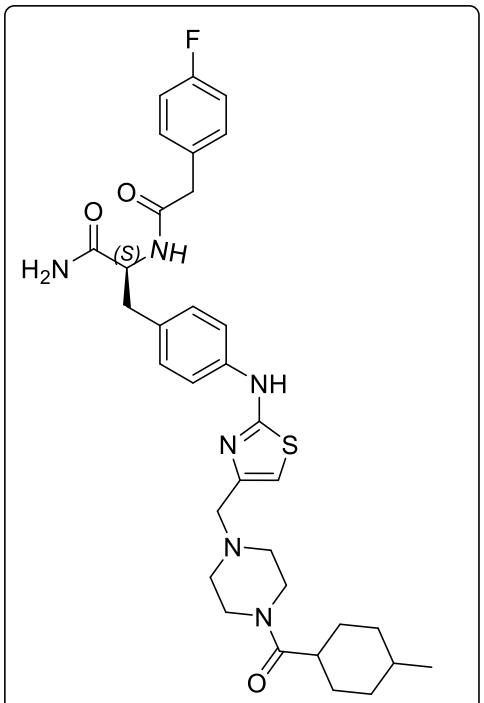
317 - 4 PURE, 300K, CDCL3




UV
1000000
500000
0
3.845
4.067
4.575
5.322
6.302
0
1
2
3
4
5
6
7


21,141,205
TIC
1/3.845
2.00
1.00
0.00
0
1
2
3
4
5
6
7


Peak 1, MH+ = 593, M+Na+ = 615
100
50
593
615
206
288
338
366
410
497
511
540
576
637
200
250
300
350
400
450
500
550
600
650
m/z



5d

$C_{33}H_{41}FN_6O_3S$

Exact Mass: 620.29

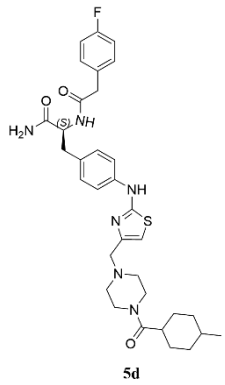
Mol. Wt.: 620.78

5d (^{1}H NMR, 400 MHz, $CDCl_3$, 300 K) δ 7.20 (d, J = 8.2 Hz, 2H), 7.15 (t, J = 6.7 Hz, 2H), 7.06 (d, J = 8.2 Hz, 2H), 7.01 (t, J = 7.5 Hz, 2H), 6.50 (s, 1H), 6.25 (d, J = 8.2 Hz, 1H), 6.02 ($s_{(broad)}$, 1H), 5.71 ($s_{(broad)}$, 1H), 4.67 (q, J = 8.2 Hz, 1H), 3.71 – 3.68 (m, 2H), 3.67 – 3.58 (m, 4H), 3.53 (s, 3H), 3.00 (d, J = 9.8 Hz, 2H), 2.60 – 2.51 (m, 5H), 1.86 – 1.73 (m, 4H), 1.54 – 1.50 (m, 4H), 0.98 (d, J = 8.9 Hz, 2H), 0.90 (d, J = 7.2 Hz, 2H)

5d (^{13}C NMR, 100 MHz, $CDCl_3$, 300 K) δ 174.6, 172.7, 170.8, 164.7, 139.2, 130.9, 130.8, 130.7, 130.2, 118.2, 116.0, 115.7, 105.7, 77.2, 53.9, 42.6, 40.1, 38.8, 37.3, 34.5, 32.1, 31.1, 29.3, 28.4, 24.9, 22.6, 18.9

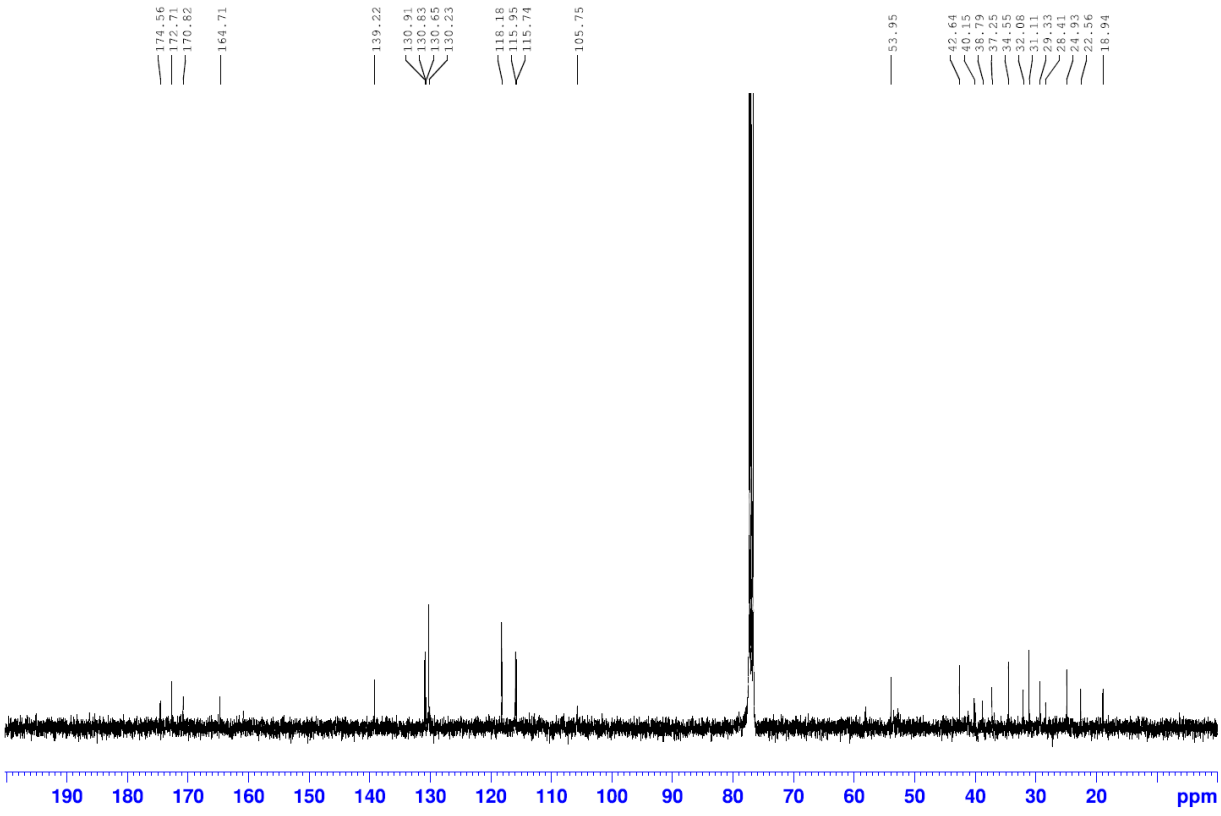
LCMS: $C_{33}H_{41}FN_6O_3S$ (M calculated) 620.78, $C_{33}H_{42}FN_6O_3S$ (MH^+ found) 621

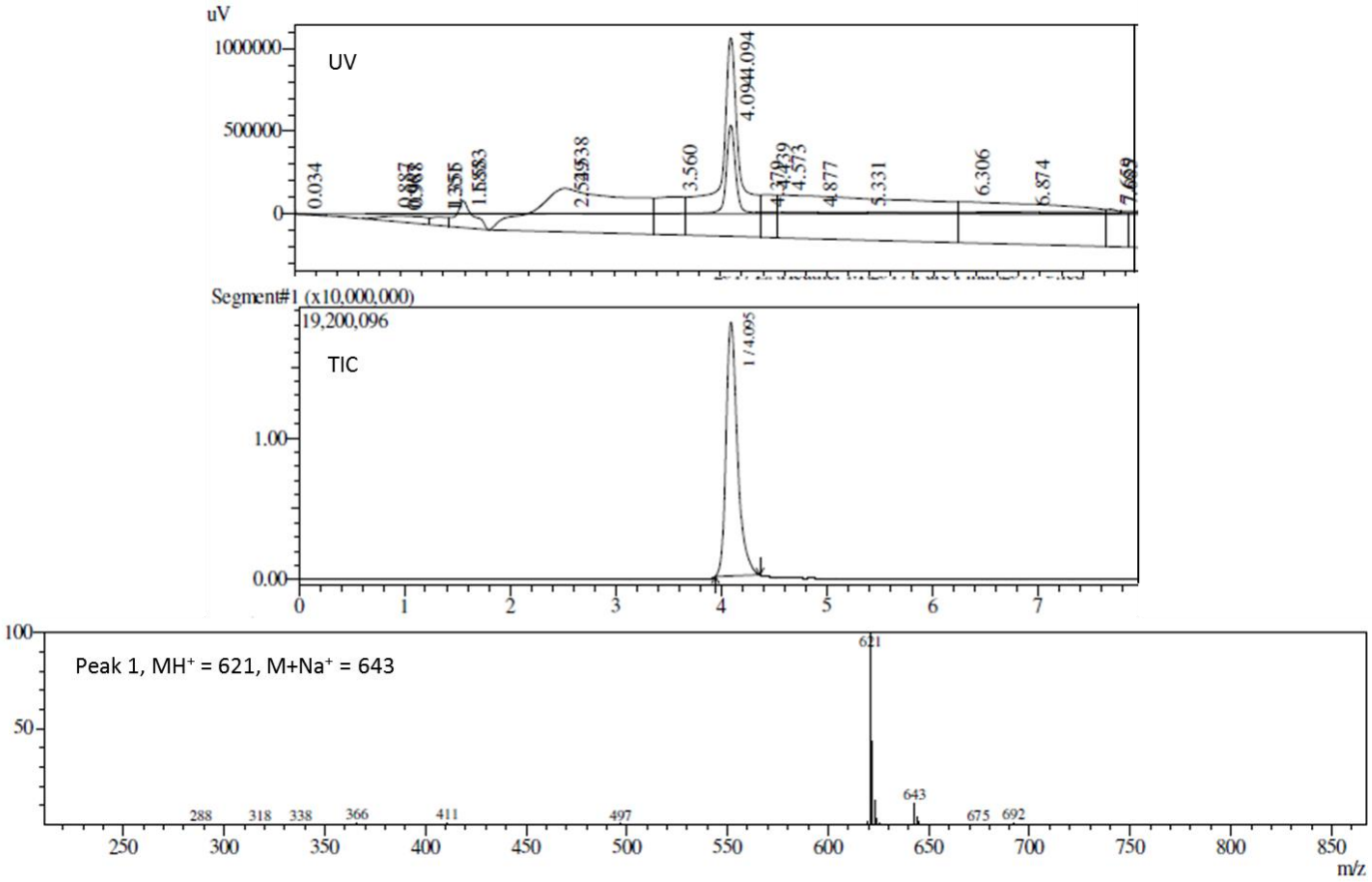
3317 - 5 PURE, 300K, CDCL3

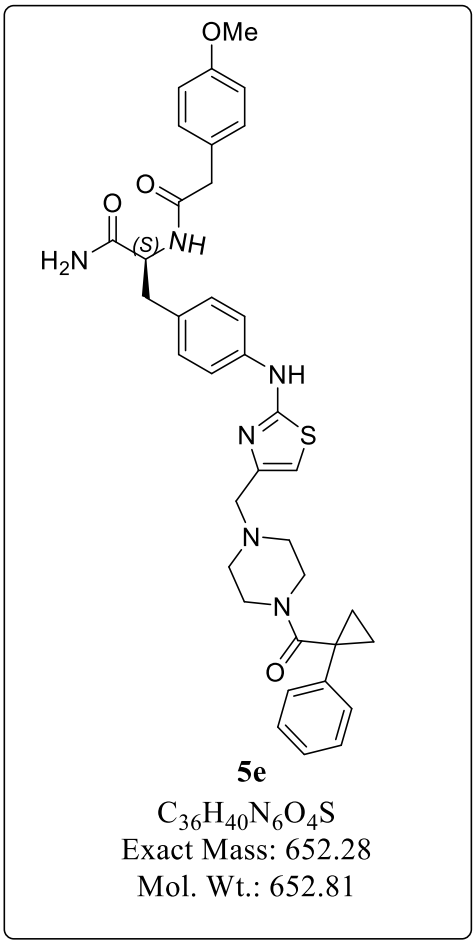


5d

3317 - 5 PURE, 300K, CDCL3




uV
1000000
500000
0
UV
0.034
3.560
4.094
4.877
5.331
6.306
6.874
Segment#1 (x10,000,000)
19,200,096
TIC
1.00
0.00
0
1
2
3
4
5
6
7
100
50
Peak 1, MH+ = 621, M+Na+ = 643
621
643
288
318
338
366
411
497
675
692
250
300
350
400
450
500
550
600
650
700
750
800
850
m/z



5e

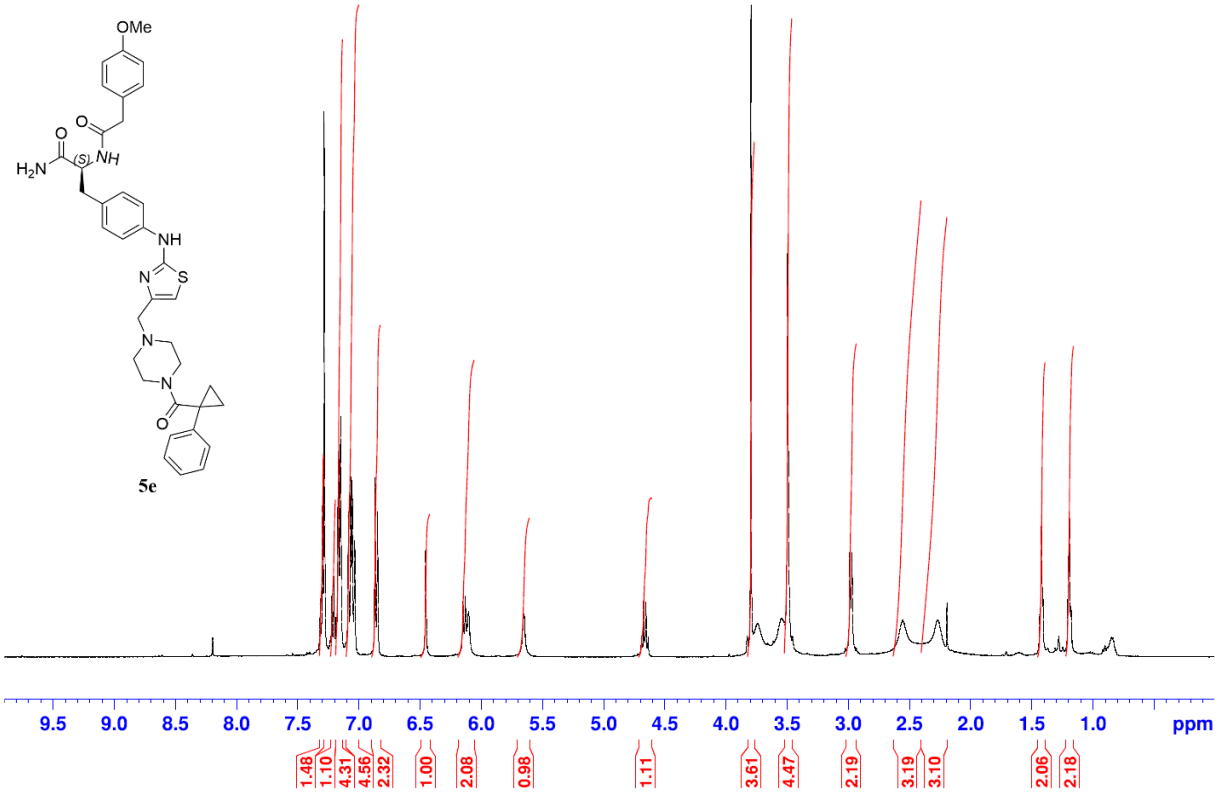
$C_{36}H_{40}N_6O_4S$
Exact Mass: 652.28
Mol. Wt.: 652.81

5e (^{1}H NMR, 400 MHz, $CDCl_3$, 300 K) δ 7.30 (t, J = 6.9 Hz, 1H), 7.21 (d, J = 8.4 Hz, 1H), 7.16 (d, J = 8.4 Hz, 4H), 7.08 (d, J = 6.8 Hz, 2H), 7.05 (d, J = 8.4 Hz, 2H), 6.86 (d, J = 8.4 Hz, 2H), 6.45 (s, 1H), 6.14 (d, J = 9.9 Hz, 1H), 6.10 ($s_{(broad)}$, 1H), 5.65 ($s_{(broad)}$, 1H), 4.66 (q, J = 7.6 Hz, 1H), 3.80 (s, 3H), 3.74 ($s_{(broad)}$, 2H), 3.55 ($s_{(broad)}$, 2H), 3.50 (s, 3H), 2.98 (d, J = 6.5 Hz, 2H), 2.55 ($s_{(broad)}$, 2H), 2.26 ($s_{(broad)}$, 2H), 1.44 – 1.42 (m, 2H), 1.21 – 1.18 (m, 2H)

5e (^{13}C NMR, 100 MHz, $CDCl_3$, 300 K) δ 172.8, 171.6, 171.0, 164.9, 159.0, 140.6, 139.1, 130.9, 130.4, 130.3, 128.7, 126.4, 126.2, 125.3, 118.3, 114.5, 77.2, 57.9, 55.3, 53.9, 52.4, 42.7, 37.0, 29.3, 15.1

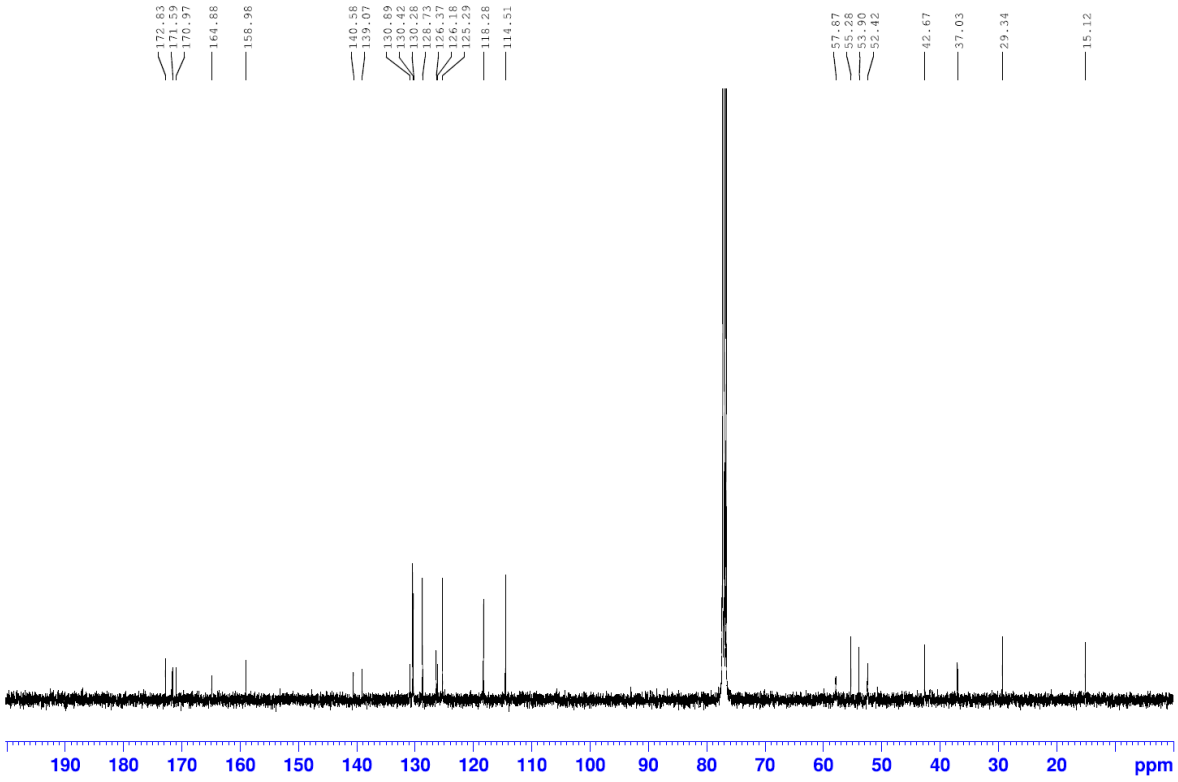
LCMS: $C_{36}H_{40}N_6O_4S$ (M calculated) 652.81, $C_{36}H_{41}N_6O_4S$ (MH^+ found) 653

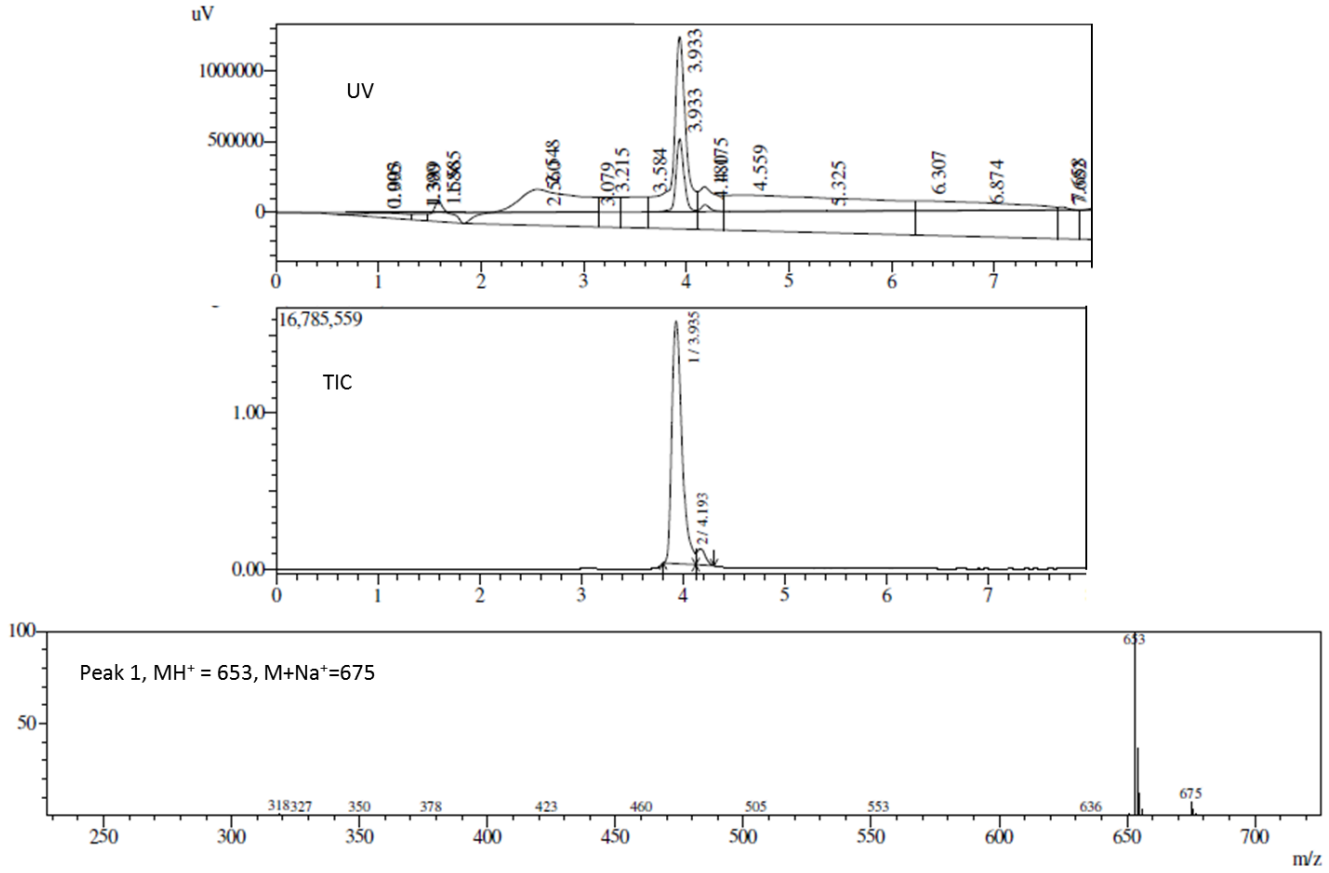
317 - 6 PURE, 300K, CDCL3

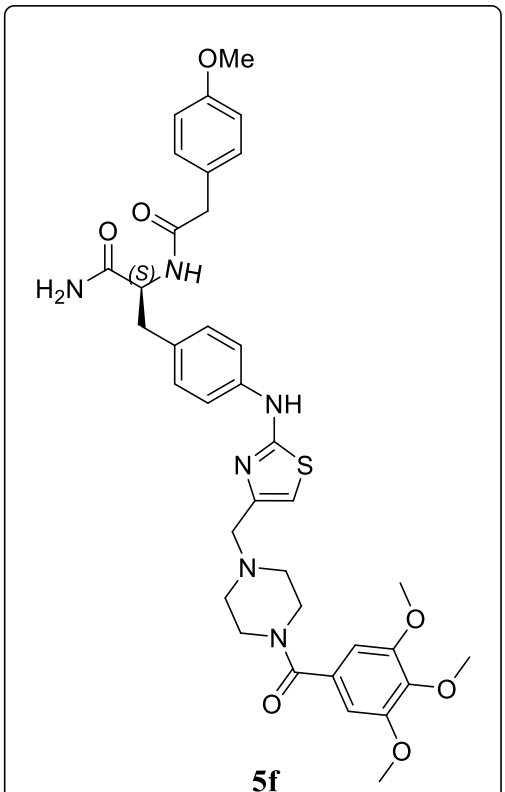


5e

2317 - 6 PURE, 300K, CDCL3




uV
1000000
500000
0
UV
3.933
3.933
3.079
3.215
3.584
4.559
5.325
6.307
6.874
0
1
2
3
4
5
6
7
16,785,559
TIC
1 / 3.935
2 / 4.193
1.00
0.00
100
50
Peak 1, MH+ = 653, M+Na+=675
653
675
318327
350
378
423
460
505
553
636
250
300
350
400
450
500
550
600
650
700
m/z



5f

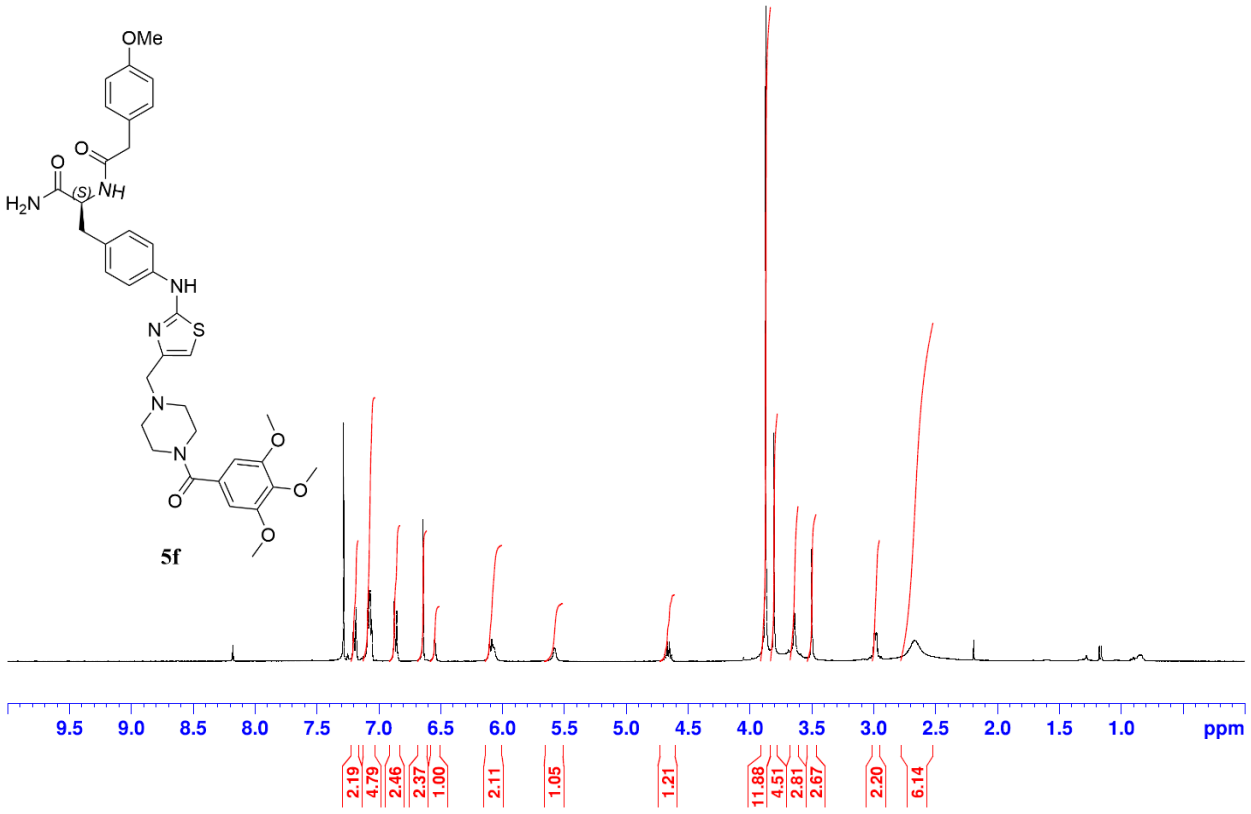
$C_{36}H_{42}N_6O_7S$
Exact Mass: 702.28
Mol. Wt.: 702.82

5f (^{1}H NMR, 400 MHz, $CDCl_3$, 300 K) δ 7.19 (d, J = 9.1 Hz, 2H), 7.08 (d, J = 6.1 Hz, 2H), 7.06 (d, J = 4.6 Hz, 2H), 6.87 (d, J = 7.6 Hz, 2H), 6.64 (s, 2H), 6.55 ($s_{(broad)}$, 1H), 6.10 (d, J = 5.4 Hz, 1H), 6.07 ($s_{(broad)}$, 1H), 5.58 ($s_{(broad)}$, 1H), 4.66 (q, J = 8.4 Hz, 1H), 3.87 (s, 3H), 3.80 (s, 4H), 3.64 ($s_{(broad)}$, 2H), 3.50 ($s_{(broad)}$, 2H), 3.01 – 2.96 (m, 2H), 2.66 ($s_{(broad)}$, 6H)

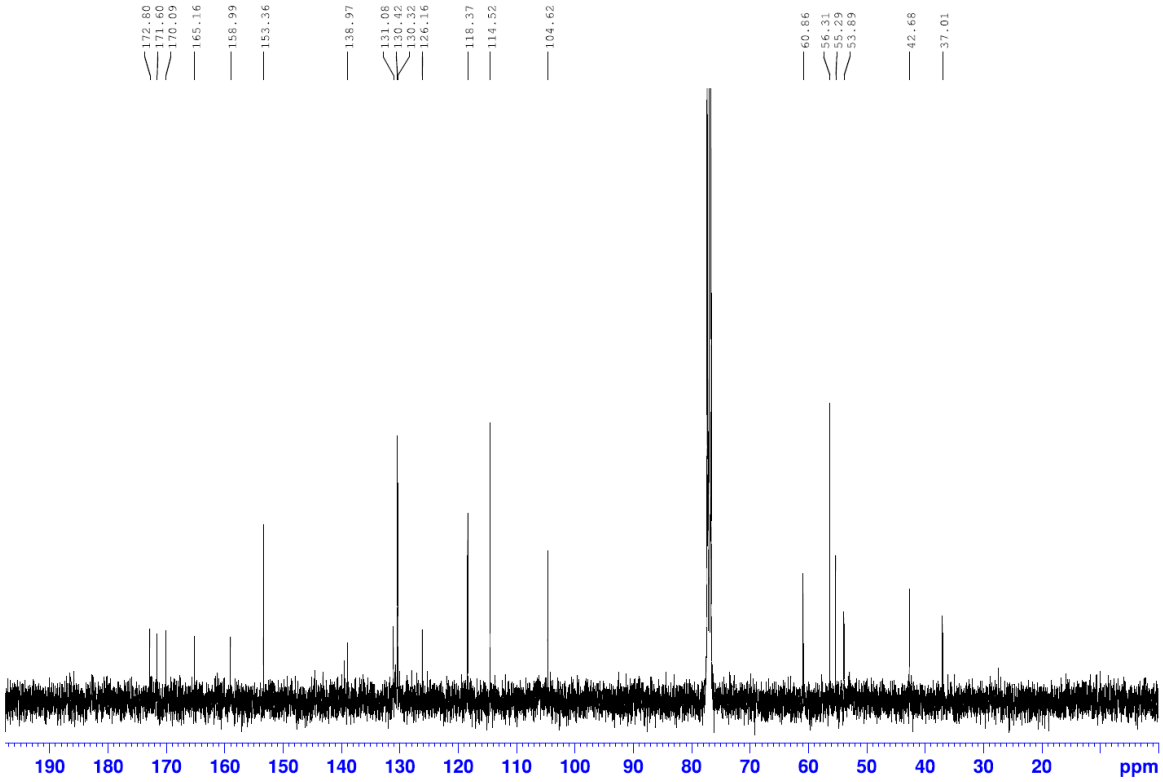
5f (^{13}C NMR, 100 MHz, $CDCl_3$, 300 K) δ 172.8, 171.6, 170.1, 165.2, 159.0, 153.4, 139.0, 131.1, 130.4, 130.3, 126.2, 118.4, 114.5, 104.6, 77.2, 60.9, 56.3, 55.3, 42.7, 37.0

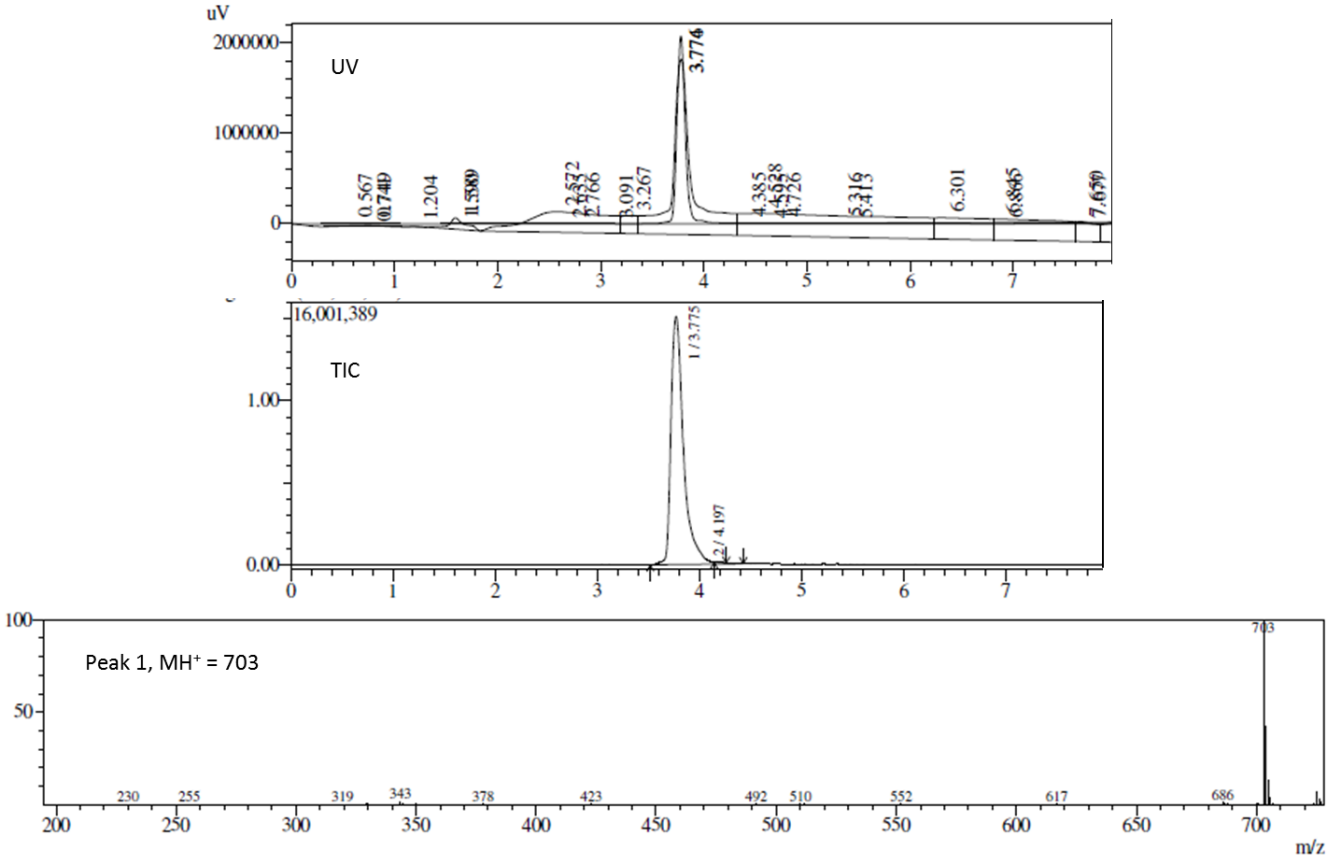
LCMS: $C_{36}H_{42}N_6O_7S$ (M calculated) 702.82, $C_{36}H_{43}N_6O_7S$ (MH^+ found) 703

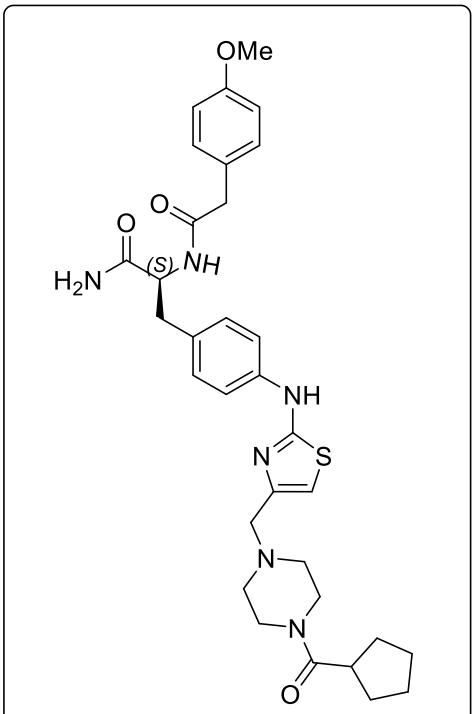
2317 - 8 PURE, 300K, CDCL3



317 - 8 PURE, 300K, CDCL3




uV
2000000
1000000
0
UV
3.774
0.567
1.204
3.267
6.301
0
1
2
3
4
5
6
7
16,001,389
TIC
1 / 3.775
2 / 4.197
1.00
0.00
100
50
Peak 1, MH+ = 703
703
230
255
319
343
378
423
492
510
552
617
686
200
250
300
350
400
450
500
550
600
650
700
m/z



5g

$C_{32}H_{40}N_6O_4S$

Exact Mass: 604.28

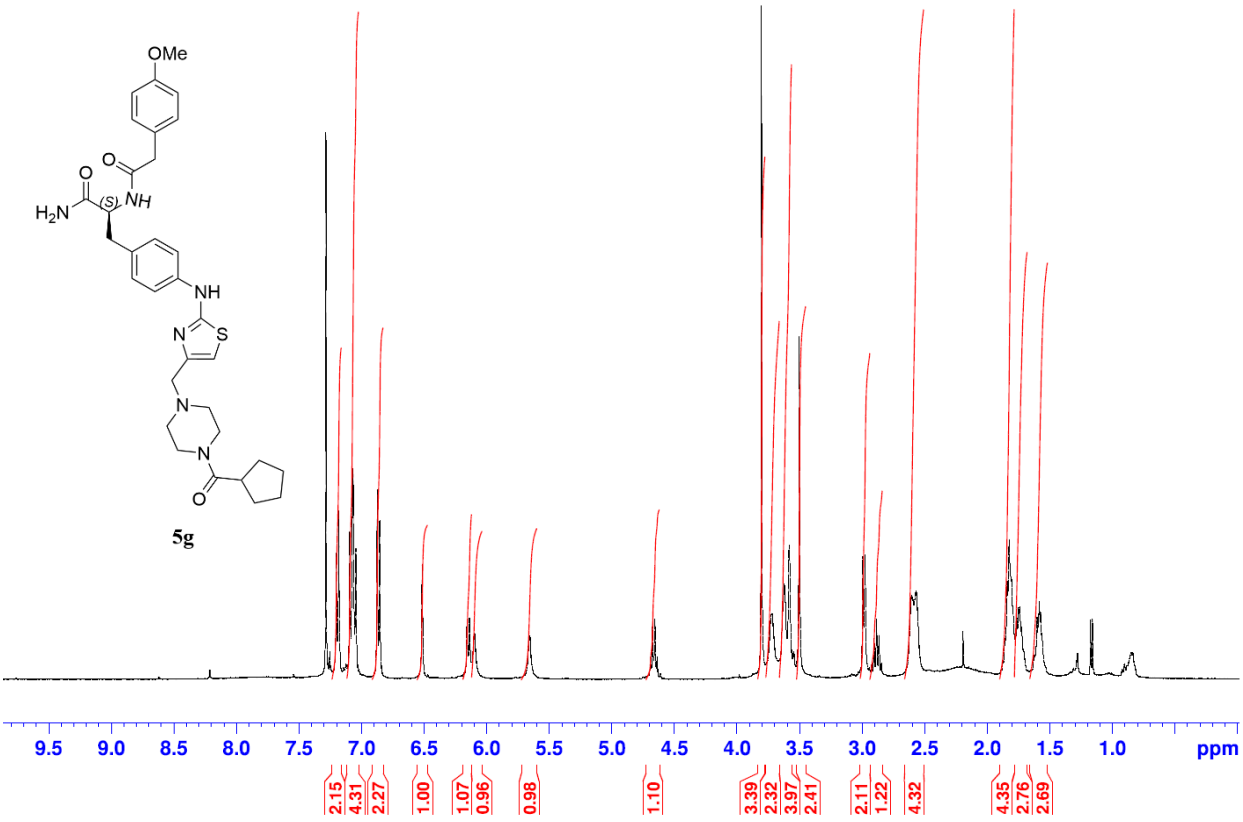
Mol. Wt.: 604.76

5g (^{1}H NMR, 400 MHz, $CDCl_3$, 300 K) δ 7.19 (d, J = 9.1 Hz, 2H), 7.08 (d, J = 6.1 Hz, 2H), 7.06 (d, J = 4.6 Hz, 2H), 6.52 ($s_{(broad)}$, 1H), 6.15 (d, J = 5.4 Hz, 1H), 6.10 ($s_{(broad)}$, 1H), 5.66 ($s_{(broad)}$, 1H), 4.67 (q, J = 8.4 Hz, 1H), 3.80 (s, 3H), 3.73 ($s_{(broad)}$, 2H), 3.66 – 3.56 (m, 4H), 3.51 (s, 2H), 2.99 (d, J = 6.9 Hz, 2H), 2.88 (pent. J = 7.7 Hz, 1H), 2.64 – 2.52 (m, 4H), 1.89 – 1.69 (m, 7H), 1.64 – 1.52 (m, 3H)

5g (^{13}C NMR, 100 MHz, $CDCl_3$, 300 K) δ 174.5, 172.8, 171.6, 164.9, 159.0, 139.1, 130.9, 130.4, 130.3, 126.2, 118.3, 114.5, 77.2, 58.0, 55.3, 53.9, 52.7, 45.1, 42.7, 41.0, 37.0, 30.1, 26.0

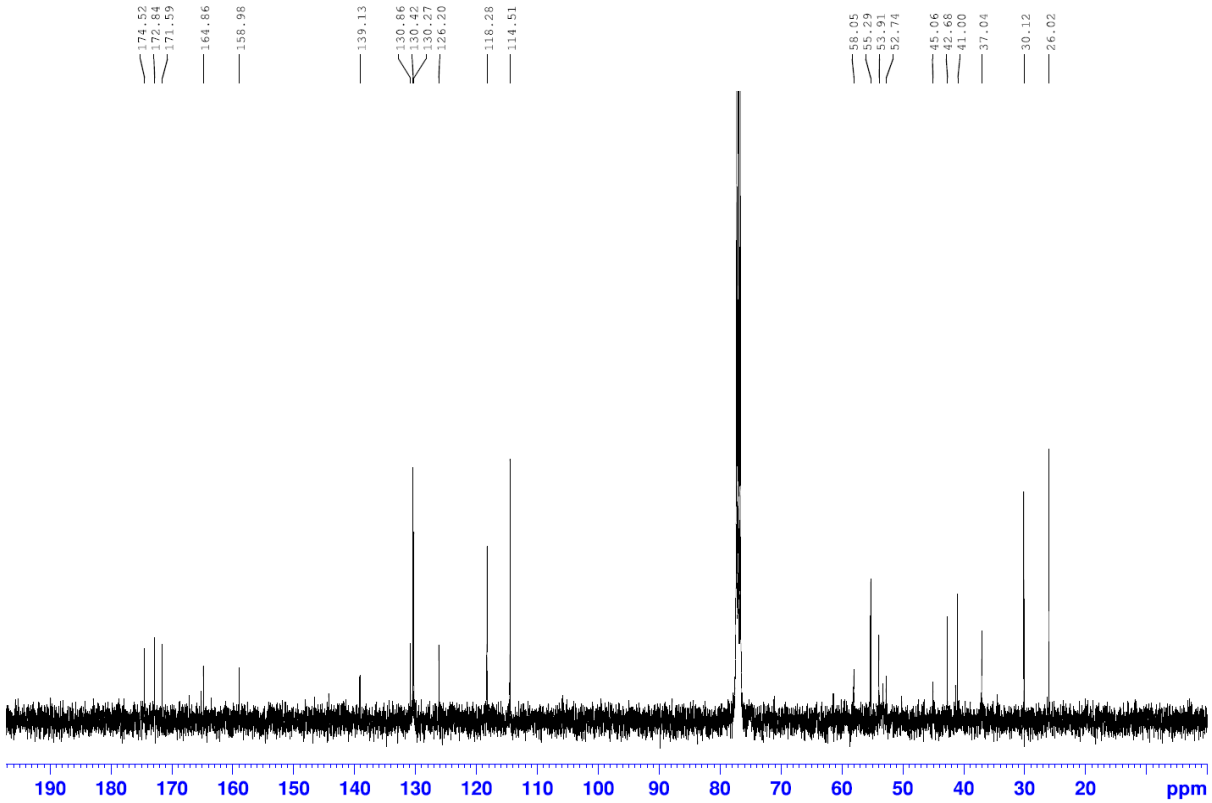
LCMS: $C_{32}H_{40}N_6O_4S$ (M calculated) 604.76, $C_{32}H_{41}N_6O_4S$ (MH^+ found) 605

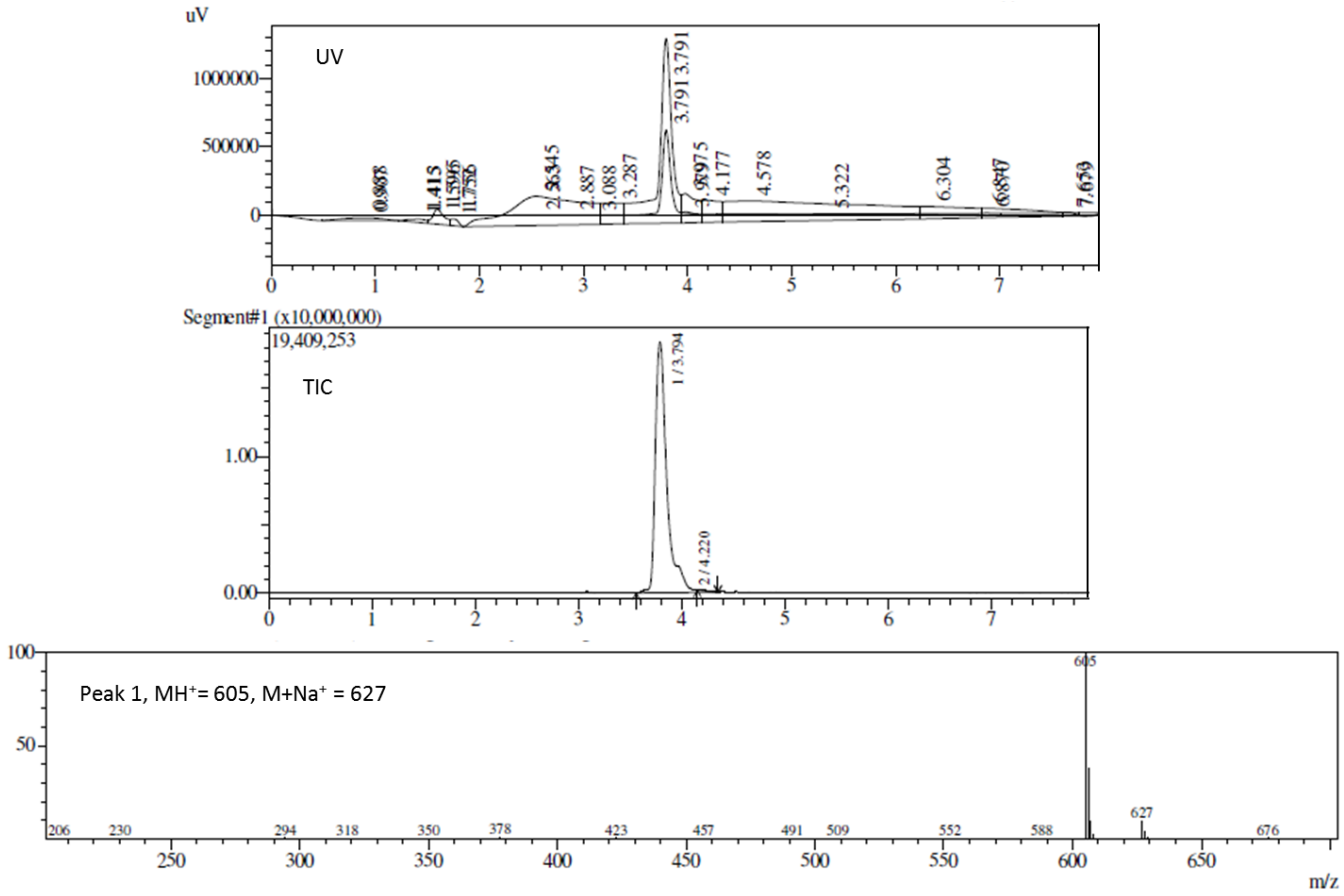
317 - 9 PURE, 300K, CDCL3

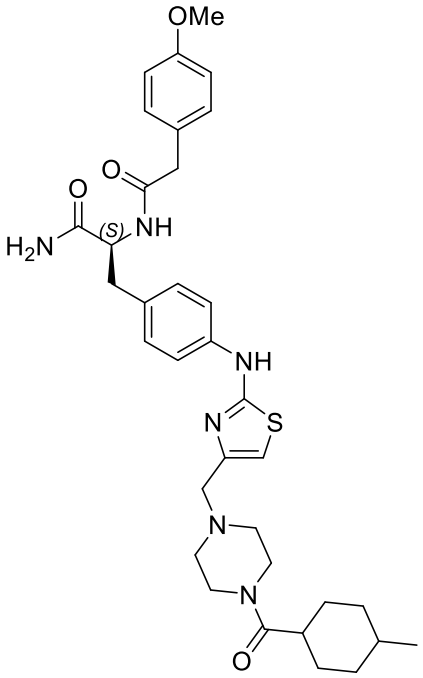


5g

317 - 9 PURE, 300K, CDCL3




uV
UV
1000000
500000
0
3.791
1.415
2.887
3.088
3.287
4.177
4.578
5.322
6.304
0 1 2 3 4 5 6 7
Segment#1 (x10,000,000)
19,409,253
TIC
1.00
0.00
1 / 3.794
2 / 4.220
0 1 2 3 4 5 6 7
100
50
Peak 1, MH+= 605, M+Na+ = 627
605
627
206 230 294 318 350 378 423 457 491 509 552 588 676
250 300 350 400 450 500 550 600 650
m/z



5h

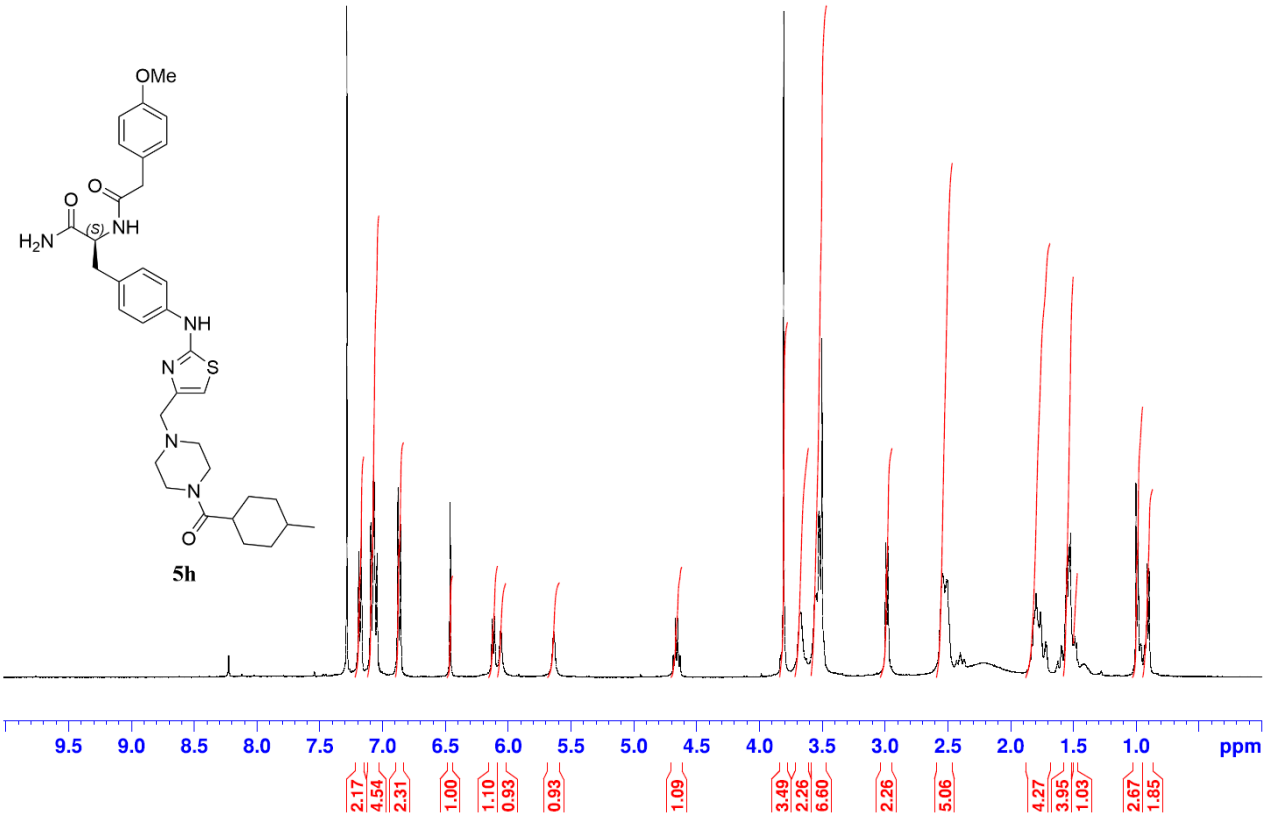
$C_{34}H_{44}N_6O_4S$
Exact Mass: 632.31
Mol. Wt.: 632.82

5h (^{1}H NMR, 400 MHz, $CDCl_3$, 300 K) δ 7.18 (d, J = 9.1 Hz, 2H), 7.09 (d, J = 6.1 Hz, 2H), 7.06 (d, J = 4.6 Hz, 2H), 6.87 (d, J = 9.0 Hz, 2H), 6.46 (s, 1H), 6.12 (d, J = 5.4 Hz, 1H), 6.06 ($s_{(broad)}$, 1H), 5.64 ($s_{(broad)}$, 1H), 4.66 (q, J = 8.4 Hz, 1H), 3.81 (s, 3H), 3.67 ($s_{(broad)}$, 2H), 3.59 – 3.51 (m, 4H), 3.51 (s, 2H), 2.98 (d, J = 6.9 Hz, 2H), 2.660 – 2.46 (m, 5H), 1.85 – 1.70 (m, 4H), 1.57 – 1.46 (m, 4H), 0.99 (d, J = 5.4 Hz, 2H), 0.90 (d, J = 5.7 Hz, 2H)

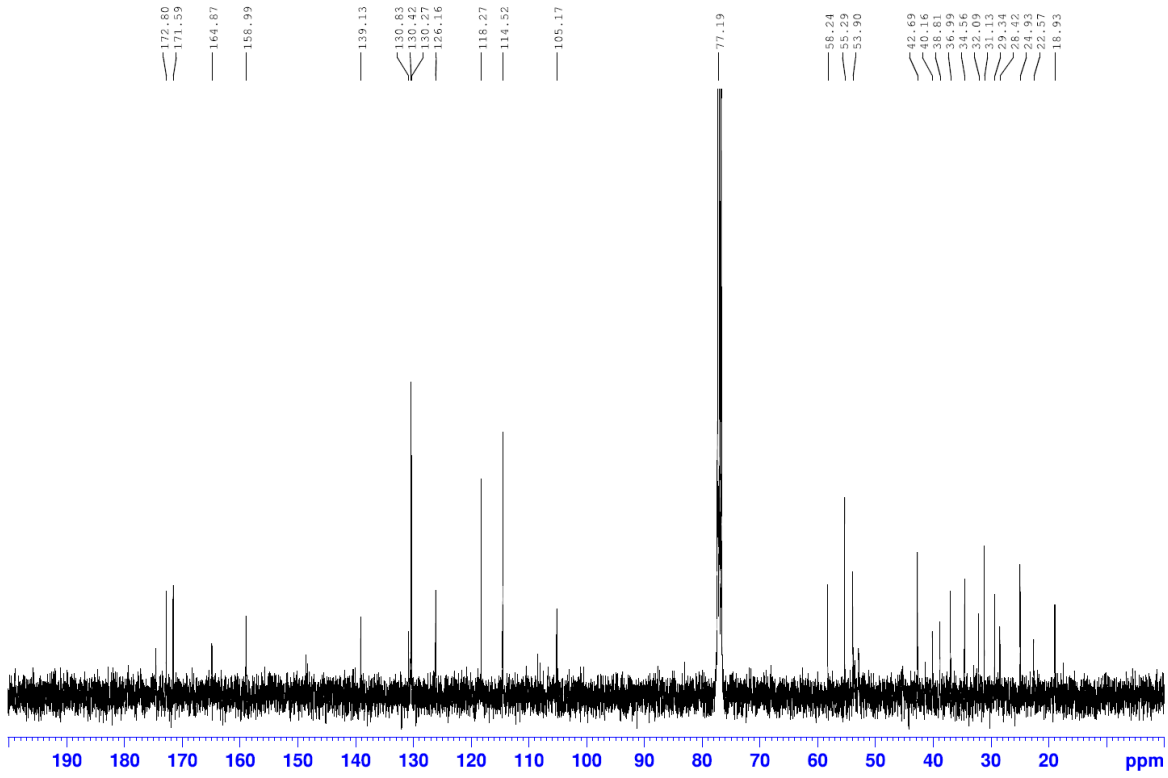
5h (^{13}C NMR, 100 MHz, $CDCl_3$, 300 K) δ 174.7, 172.8, 171.6, 164.9, 159.0, 139.1, 130.8, 130.4, 130.3, 126.2, 118.3, 114.5, 105.2, 77.2, 58.2, 55.3, 53.9, 42.7, 40.2, 38.8, 37.0, 34.6, 32.1, 29.3, 28.4, 24.9, 22.6, 18.9

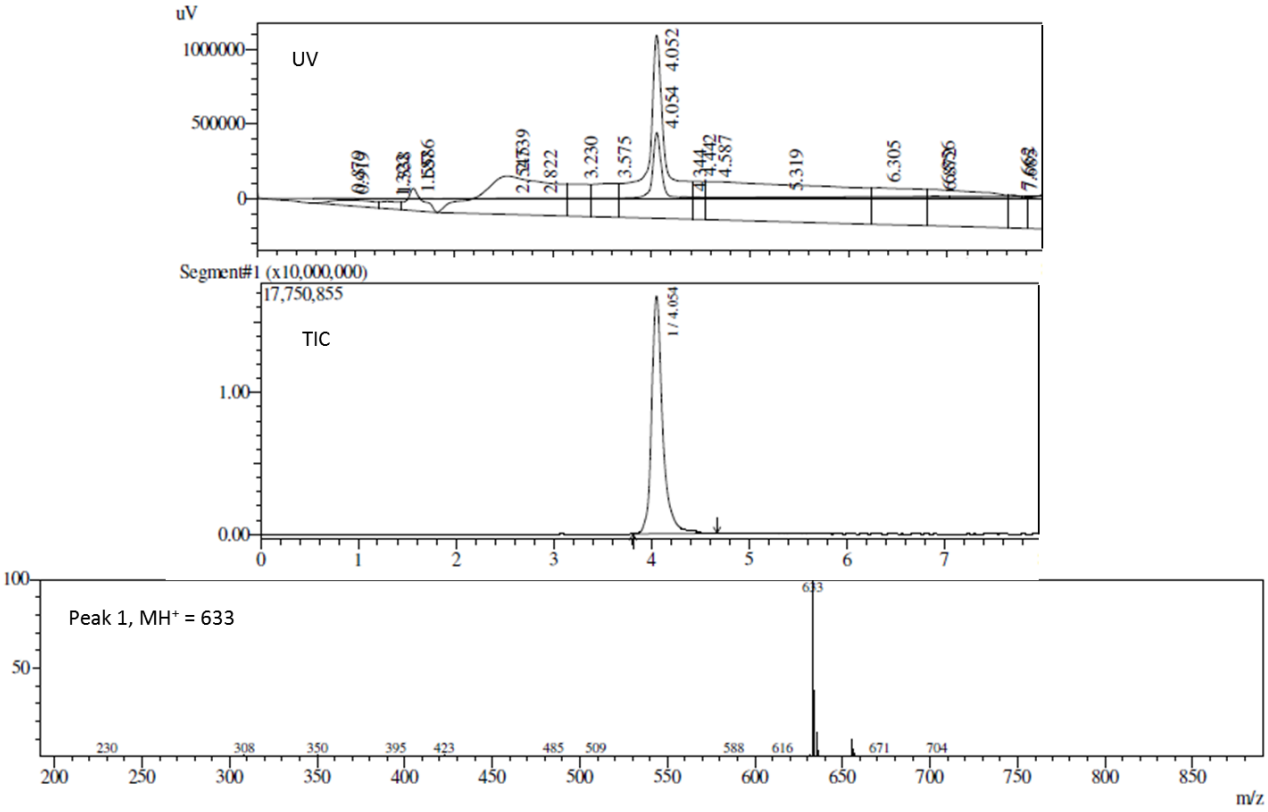
LCMS: $C_{34}H_{44}N_6O_4S$ (M calculated) 632.82, $C_{34}H_{45}N_6O_4S$ (MH^+ found) 633

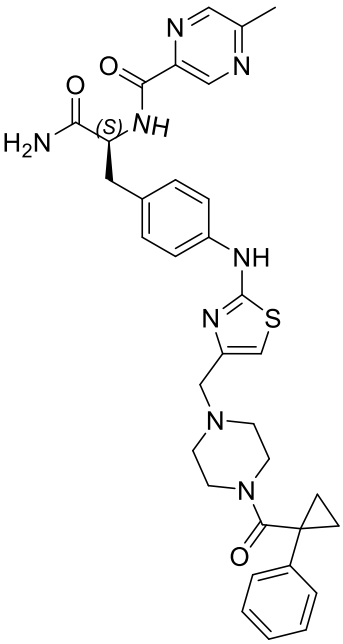
2317 - 10 PURE, 300K, CDCL3



2317 - 10 PURE, 300K, CDCL3




uV
1000000
500000
0
UV
4.052
4.054
3.230
3.575
2.822
4.587
5.319
6.305
Segment#1 (x10,000,000)
17,750,855
TIC
1 / 4.054
1.00
0.00
0
1
2
3
4
5
6
7
100
50
Peak 1, MH+ = 633
633
230
308
350
395
423
485
509
588
616
671
704
200
250
300
350
400
450
500
550
600
650
700
750
800
850
m/z



5i

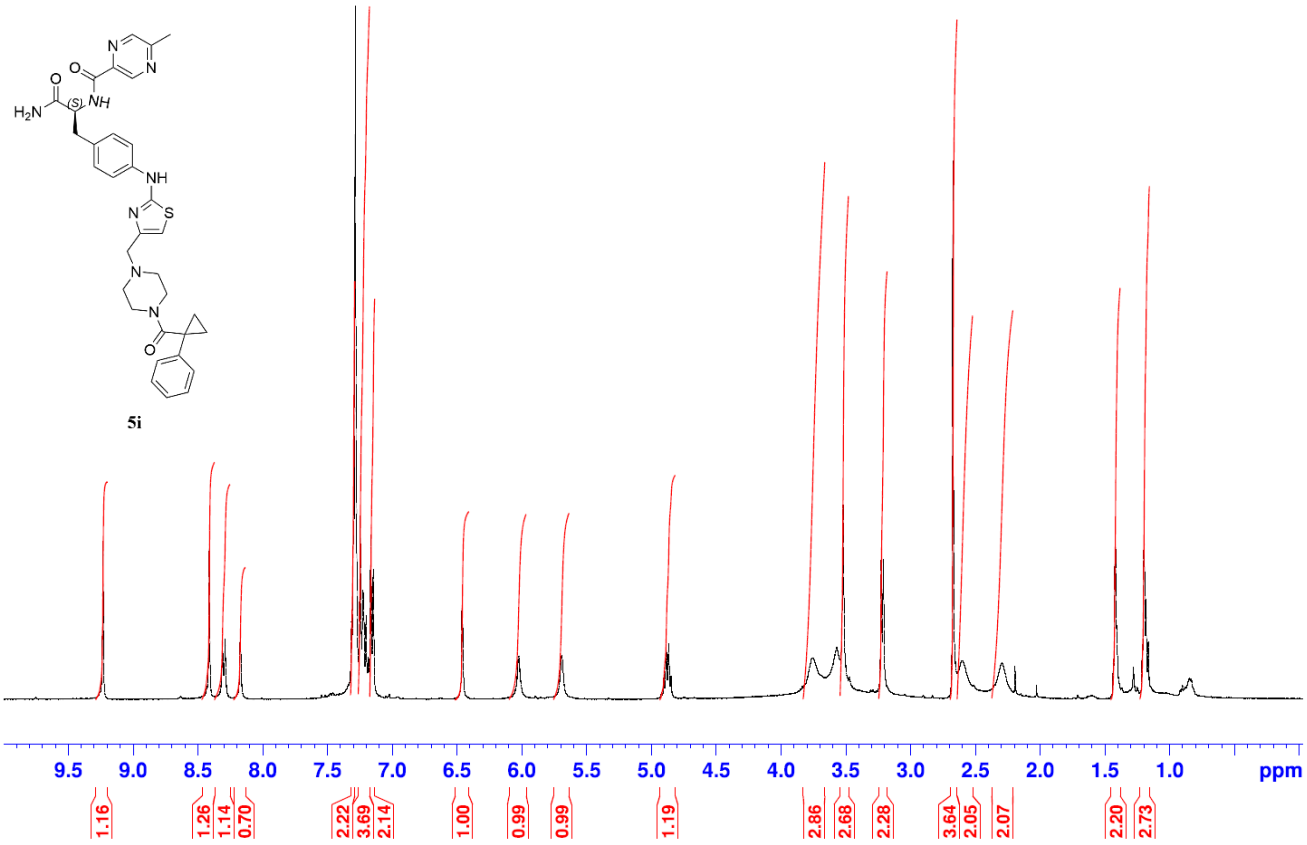
$C_{33}H_{36}N_8O_3S$
Exact Mass: 624.26
Mol. Wt.: 624.76

5i (^{1}H NMR, 400 MHz, $CDCl_3$, 300 K) δ 9.24 (s, 1H), 8.41 (s, 1H), 8.30 (d, J = 12.1 Hz, 1H), 8.17 (s, 1H), 7.31 – 7.27 (m, 4H), 7.24 (d, J = 7.1 Hz, 2H), 7.20 (t, J = 7.1 Hz, 1H), 7.16 (d, J = 10.9 Hz, 2H), 6.46 (s, 1H), 6.02 ($s_{(broad)}$, 1H), 5.69 ($s_{(broad)}$, 1H), 4.88 (q, J = 8.4 Hz, 1H), 3.76 ($s_{(broad)}$, 2H), 3.57 ($s_{(broad)}$, 2H), 3.52 (s, 2H), 3.22 (d, J = 9.1 Hz, 2H), 2.67 (s, 3H), 2.59 ($s_{(broad)}$, 2H), 2.30 ($s_{(broad)}$, 2H), 1.44 – 1.40 (m, 2H), 1.22 – 1.16 (m, 2H)

5i (^{13}C NMR, 100 MHz, $CDCl_3$, 300 K) δ 172.5, 172.2, 171.0, 165.5, 163.4, 157.6, 150.2, 143.3, 142.6, 141.1, 140.5, 139.0, 131.3, 130.4, 128.8, 126.4, 125.3, 118.5, 57.2, 54.2, 52.2, 37.5, 29.3, 21.8, 15.1

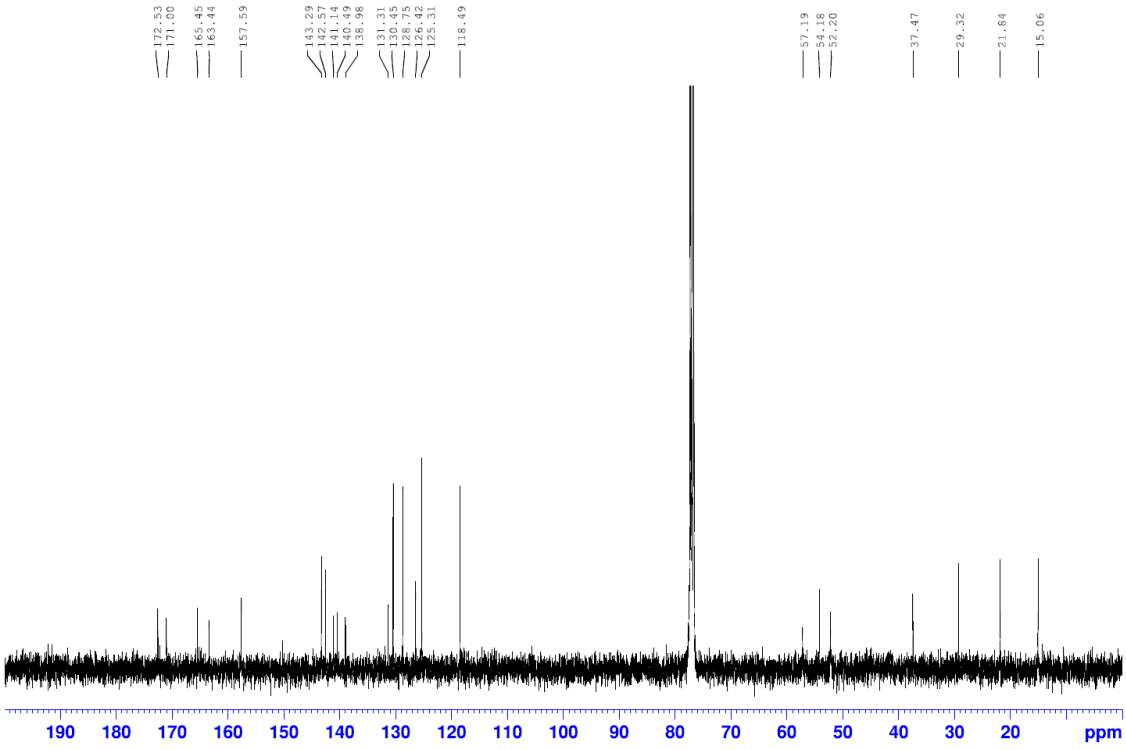
LCMS: $C_{33}H_{36}N_8O_3S$ (M calculated) 624.76, $C_{33}H_{37}N_8O_3S$ (MH^+ found) 625

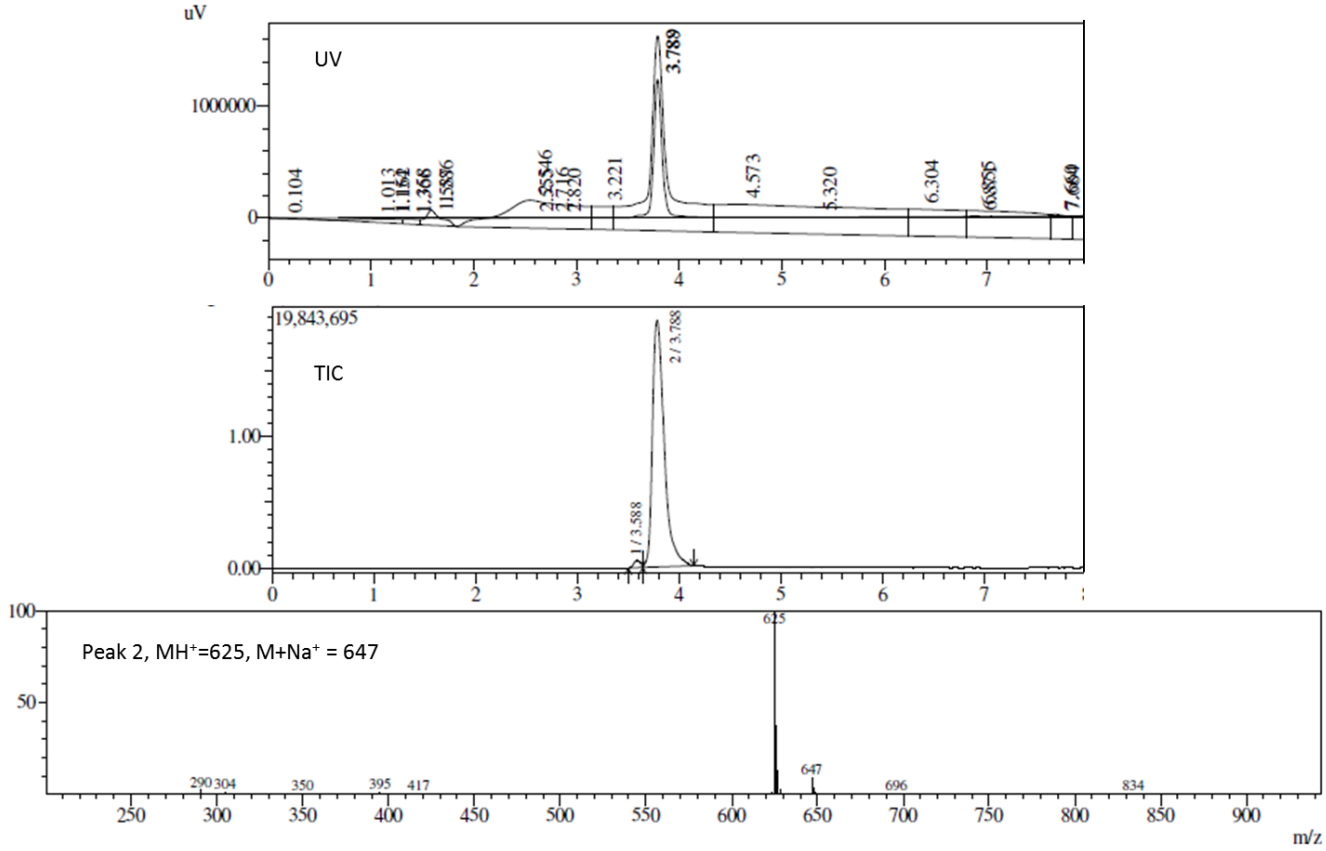
2317 - 11 PURE, 300K, CDCL3

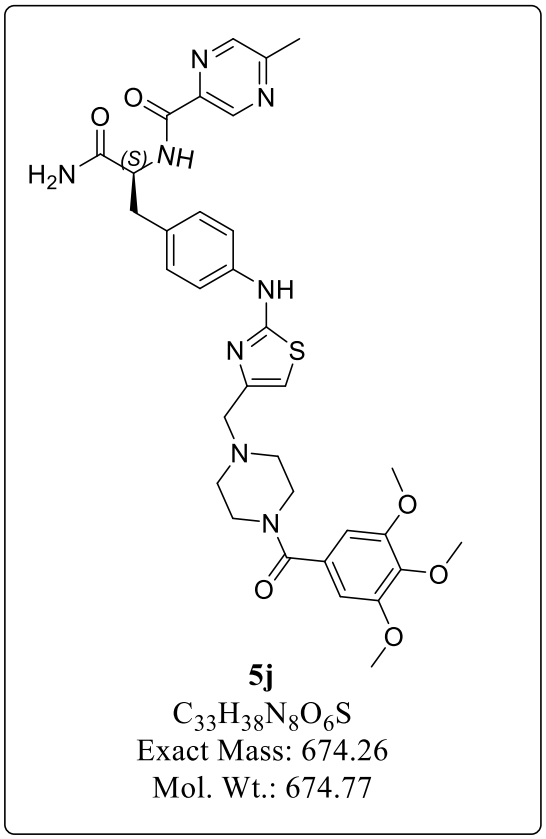


5i

2317 - 11 PURE, 300K, CDCL3




uV
UV
1000000
0
0.104
3.221
3.789
4.573
5.320
6.304
0
1
2
3
4
5
6
7
19,843,695
TIC
1.00
0.00
1 / 3.588
2 / 3.788
100
50
Peak 2, MH+=625, M+Na+ = 647
625
647
290
304
350
395
417
696
834
250
300
350
400
450
500
550
600
650
700
750
800
850
900
m/z



5j

$C_{33}H_{38}N_8O_6S$

Exact Mass: 674.26

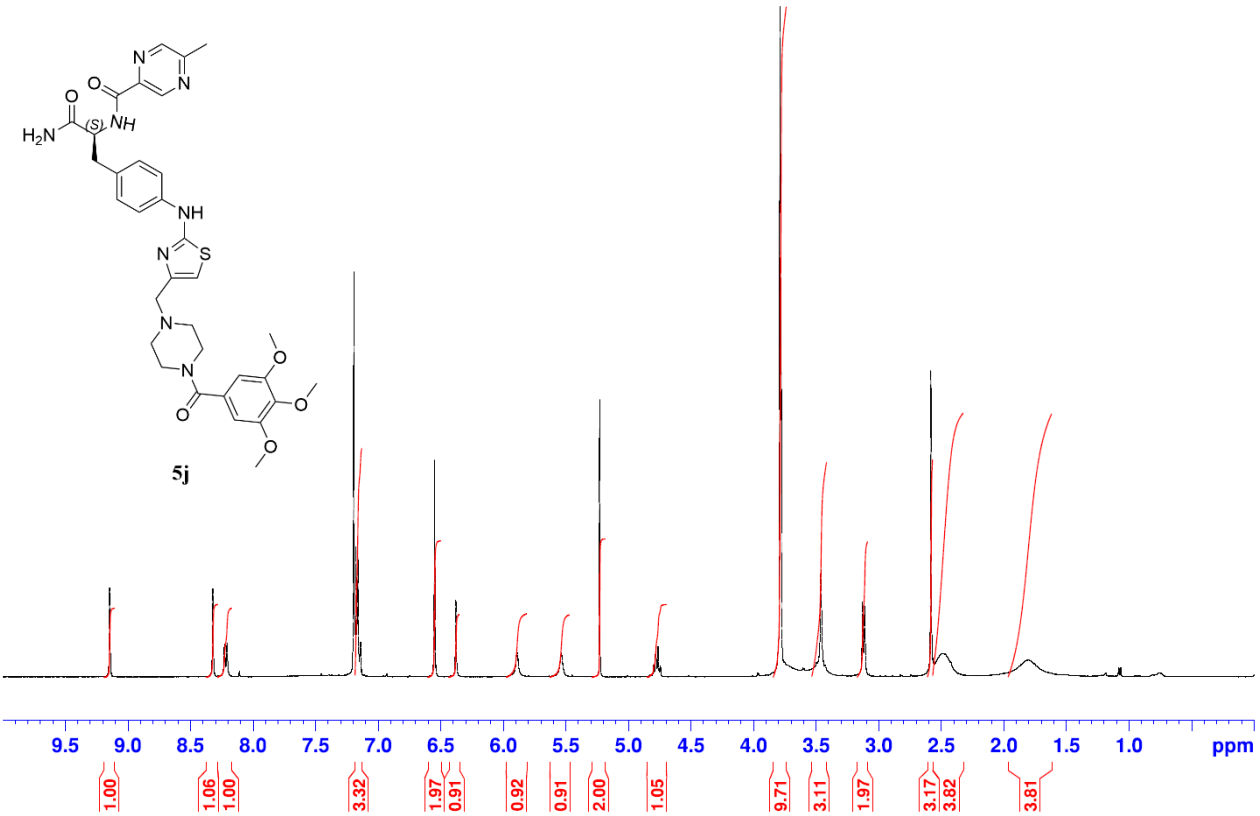
Mol. Wt.: 674.77

5j (^{1}H NMR, 400 MHz, $CDCl_3$, 300 K) δ 9.15 (s, 1H), 8.32 (s, 1H), 8.22 (d, J = 8.6 Hz, 1H), 7.17 (d, J = 5.9 Hz, 4H), 6.55 (s, 2H), 6.38 (s_{broad}, 1H), 5.90 (s_{broad} , 1H), 5.53 (s_{broad} , 1H), 5.23 (s, 2H), 4.77 (q, J = 7.6 Hz, 1H), 3.79 (s, 9H), 3.78 (s, 2H), 3.46 (s, 2H), 3.12 (d, J = 6.5 HZ, 2H), 2.58 (s, 3H), 2.48 ($s_{v.\ broad}$, 4H), 1.80 ($s_{v.broad}$, 4H)

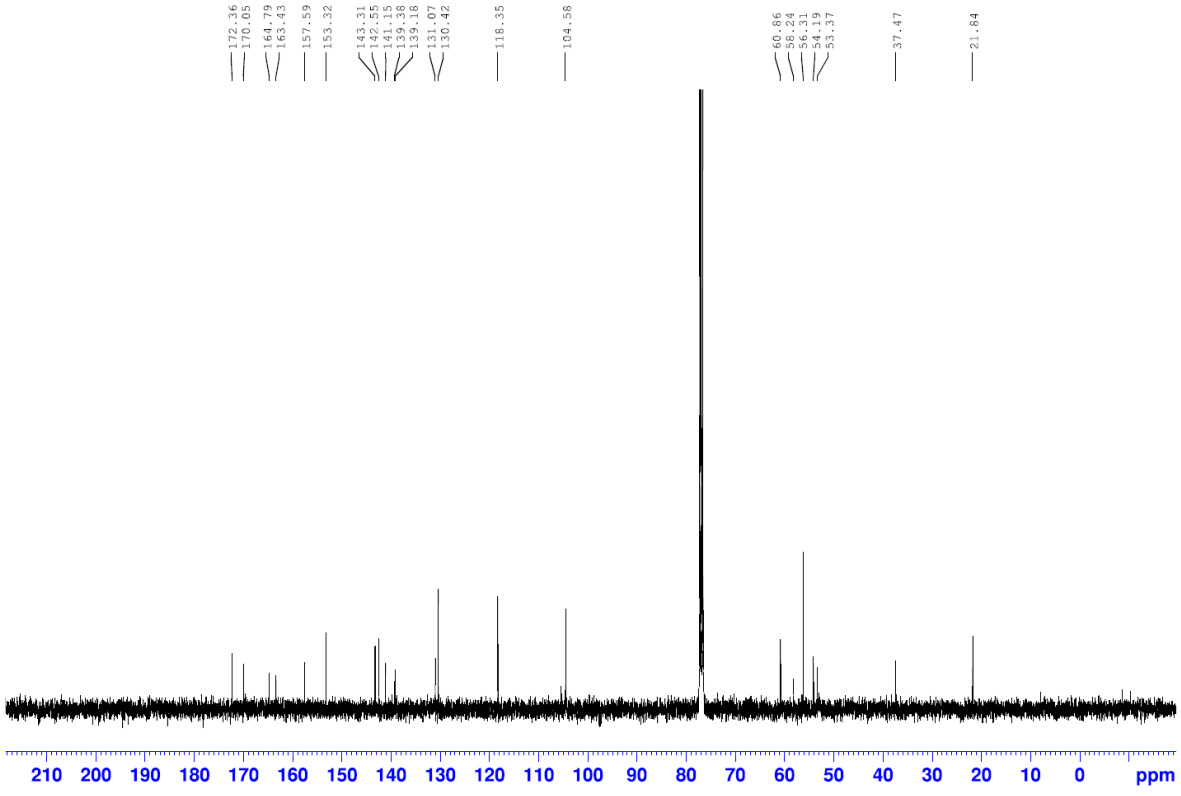
5j (^{13}C NMR, 100 MHz, $CDCl_3$, 300 K) δ 172.4, 170.1, 164.8, 163.4, 157.6, 153.3, 143.3, 142.6, 141.2, 139.4, 139.2, 131.1, 130.4, 118.3, 104.6, 60.9, 58.2, 56.3, 54.2, 53.4, 37.5, 21.8

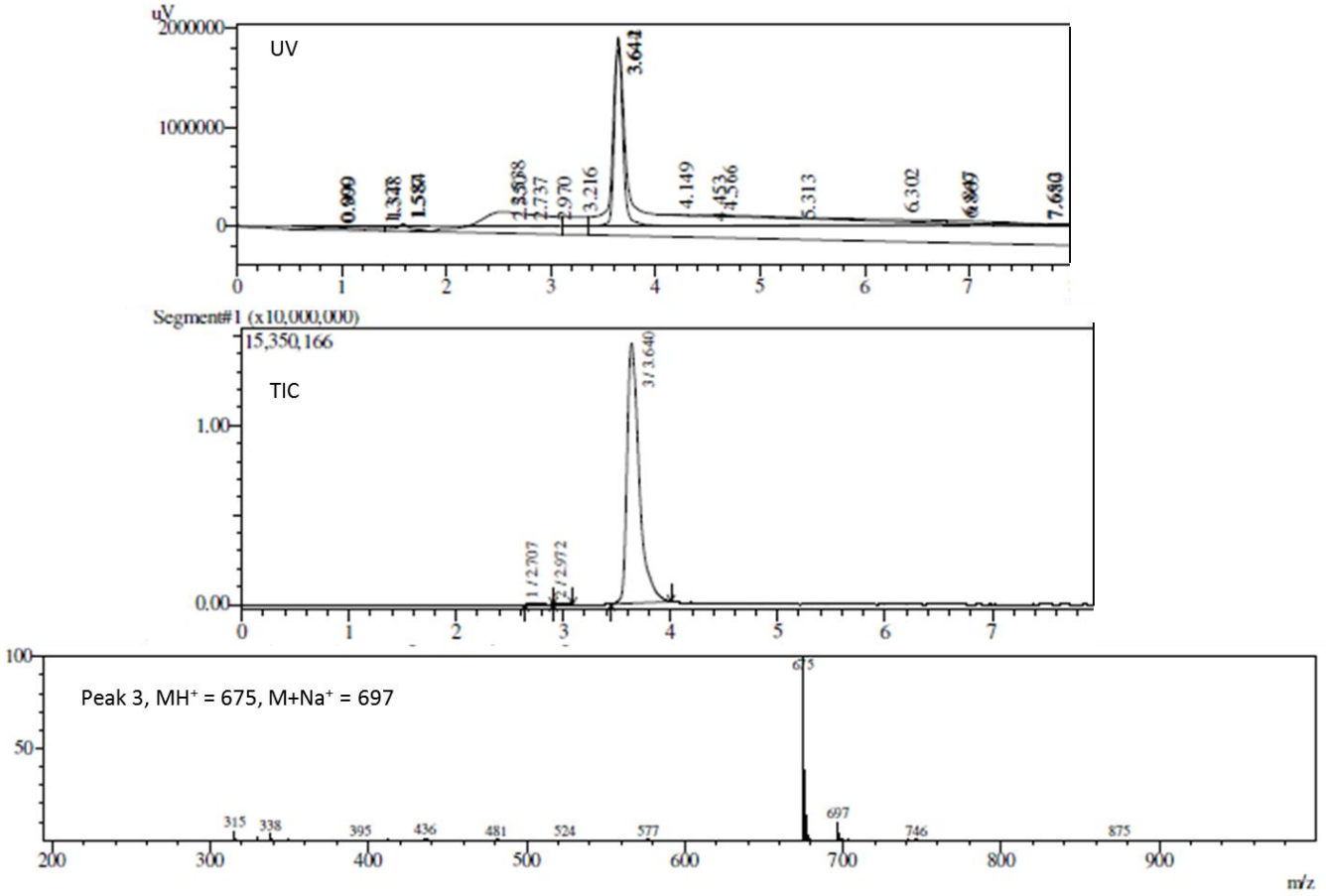
LCMS: $C_{33}H_{38}N_8O_6S$ (M calculated) 674.77, $C_{33}H_{39}N_8O_6S$ (MH^+ found) 675

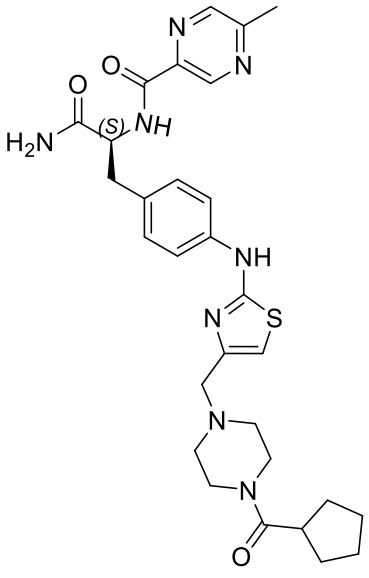
2317 - 13 PURE, 300K, CDCL3



317 - 13 PURE, 300K, CDCL3




uV
2000000
1000000
0
UV
3.641
0.899
1.338
1.581
2.737
2.970
3.216
4.149
4.566
5.313
6.302
7.680
0
1
2
3
4
5
6
7
Segment#1 (x10,000,000)
15,350,166
TIC
1.00
0.00
3 / 3.640
1 / 2.707
2 / 2.972
100
50
Peak 3, MH+ = 675, M+Na+ = 697
675
697
315
338
395
436
481
524
577
746
875
200
300
400
500
600
700
800
900
m/z



5k

$C_{29}H_{36}N_8O_3S$

Exact Mass: 576.26

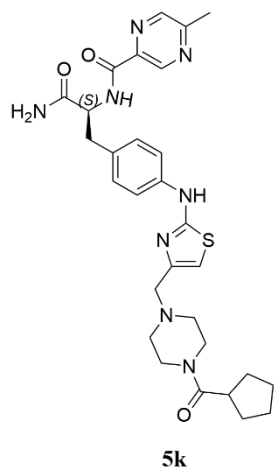
Mol. Wt.: 576.71

5k (^{1}H NMR, 400 MHz, $CDCl_3$, 300 K) δ 9.24 (s, 1H), 8.42 (s, 1H), 8.32 (d, J = 8.3 Hz, 1H), 7.26 (d, J = 6.0 Hz, 4H), 6.47 (s, 1H), 5.97 (s_{broad}, 1H), 5.64 (s_{broad} , 1H), 5. 32 (s, 2H), 4.87 (q, J = 6.8 Hz, 1H), 3.73-3.66 (m, 2H), 3.62-3.57 (m, 2H), 3.53 (s, 2H), 3.24-3.19 (m, 2H), 2.89 (pent., J = 7.6 Hz, 1H), 2.67 (s, 3H), 2.57-2.49 (m, 4H), 1.97 ($s_{v.\ broad}$, 2H), 1.86-1.70 (m, 6H), 1.63 – 1.53 (m, 2H)

5k (^{13}C NMR, 100 MHz, $CDCl_3$, 300 K) δ 174.5, 172.3, 164.8, 163.4, 157.6, 143.3, 142.6, 141.2, 139.2, 131.0, 130.4, 118.3, 58.2, 54.2, 53.4, 53.4, 52.9, 41.0, 37.5, 30.1, 26.0, 21.8

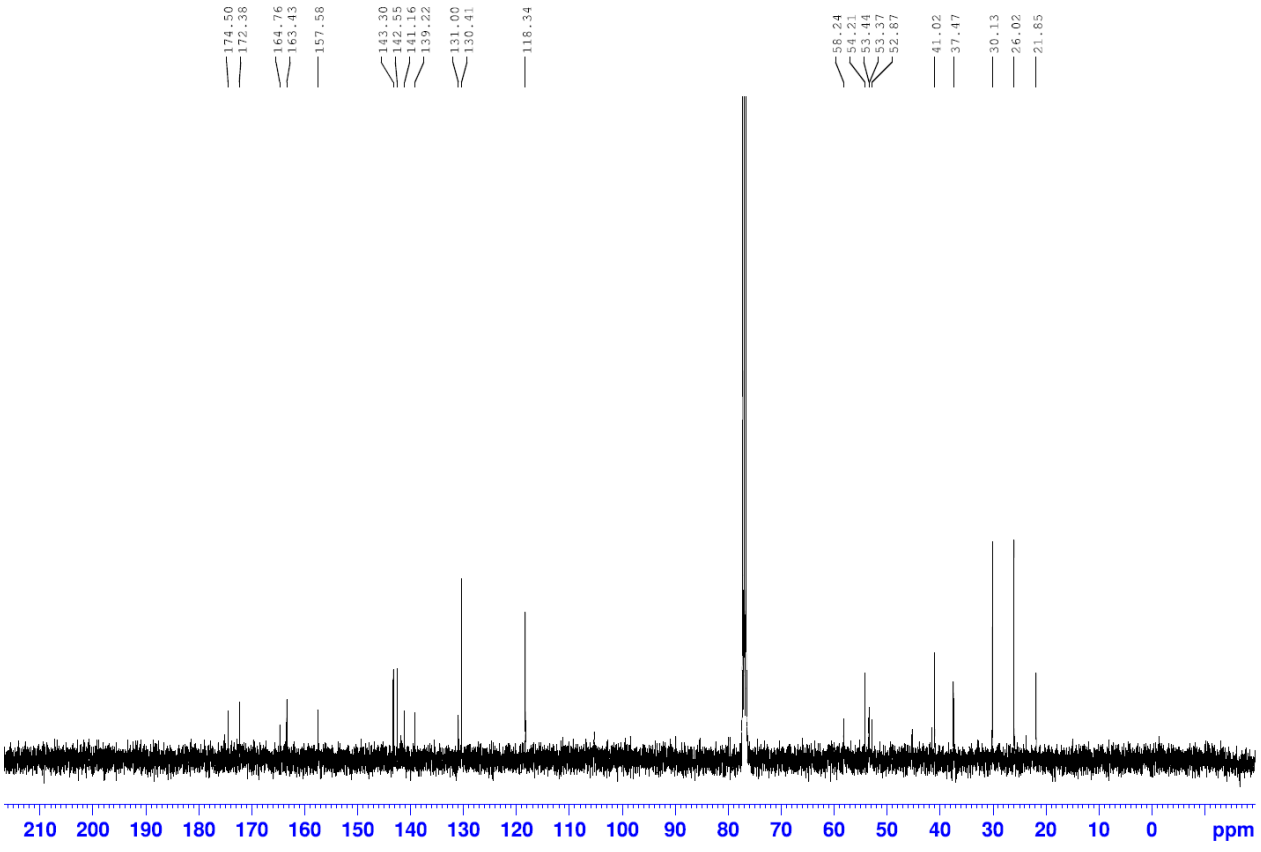
LCMS: $C_{29}H_{36}N_8O_3S$ (M calculated) 576.71, $C_{29}H_{37}N_8O_3S$ (MH^+ found) 577

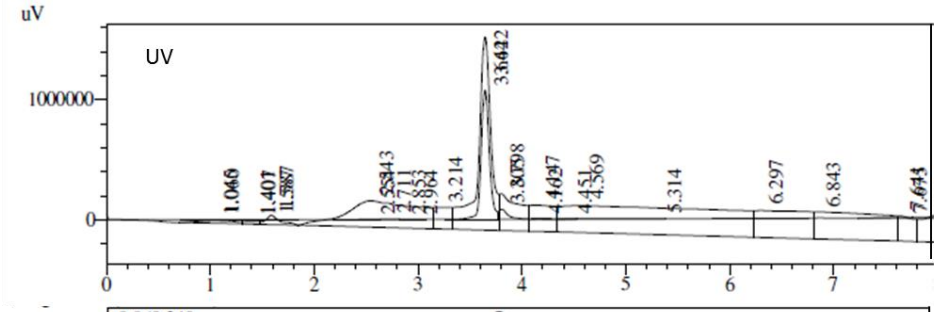
2317 - 14 PURE, 300K, CDCL3

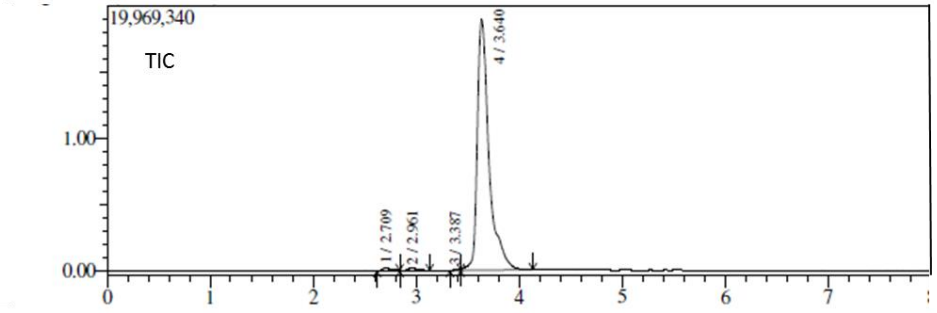


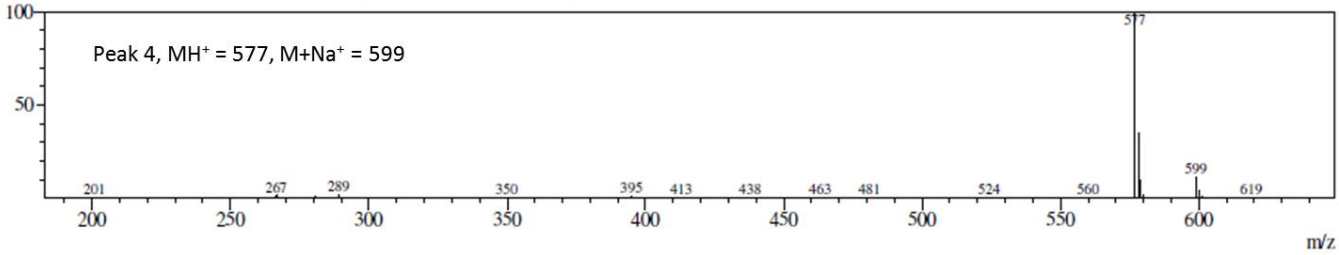
5k

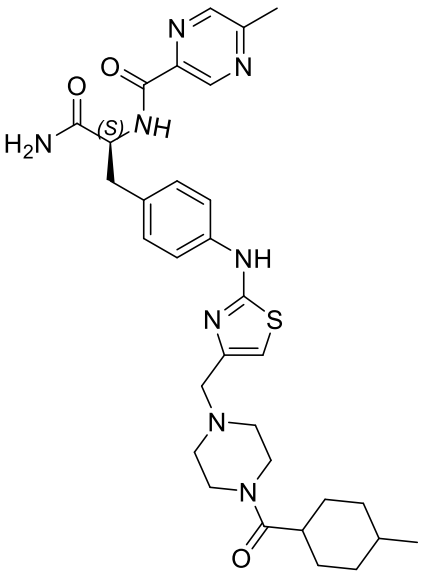
317 - 14 PURE, 300K, CDCL3




uV
UV
1000000
0
1.046
1.407
3.214
3.36422
3.80598
4.44237
4.451
4.569
5.314
6.297
6.843
7.643
0
1
2
3
4
5
6
7


19,969,340
TIC
1.00
0.00
1 / 2.709
2 / 2.961
3 / 3.387
4 / 3.640
0
1
2
3
4
5
6
7


100
50
Peak 4, MH+ = 577, M+Na+ = 599
577
599
201
267
289
350
395
413
438
463
481
524
560
619
200
250
300
350
400
450
500
550
600
m/z



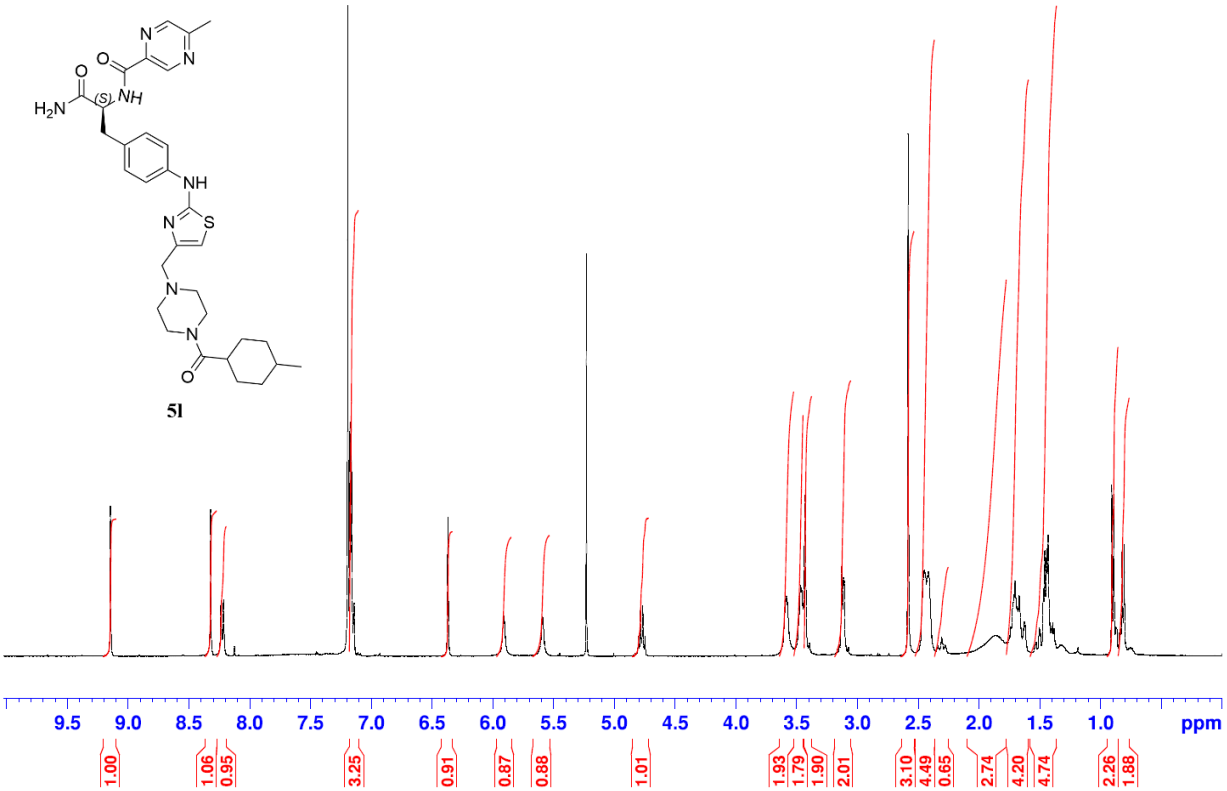
5l
$C_{31}H_{40}N_8O_3S$
Exact Mass: 604.29
Mol. Wt.: 604.77

5l (^{1}H NMR, 400 MHz, $CDCl_3$, 300 K) δ 9.14 (s, 1H), 8.32 (s, 1H), 8.23 (d, J = 8.4 Hz, 1H), 7.17 (d, J = 4.9 Hz, 4H), 6.37 (s, 2H), 5.91 (s_{broad}, 1H), 5.59 (s_{broad} , 1H), 5.53 (s_{broad} , 1H), 5.23 (s, 2H), 4.78 (q, J = 8.3 Hz, 1H), 3.59 (s_{broad}, 2H), 3.47 (s_{broad} , 2H), 3.43 (s, 2H), 3.14-3.10 (m, 2H), 2.58 (s, 3H), 2.49-2.38 (m, 2H), 1.86 ($s_{v.\ broad}$, 4H), 1.76 – 1.70 (m, 4H), 1.51-1.37 (m, 4H), 0.90 (d, J = 6.8 Hz, 2H), 0.81 (d, J = 6.6 Hz, 2H)

5l (^{13}C NMR, 100 MHz, $CDCl_3$, 300 K) δ 174.5, 172.4, 164.7, 163.4, 157.6, 143.3, 142.6, 141.2, 139.2, 131.0, 130.4, 118.3, 105.4, 58.3, 54.2, 53.6, 41.4, 40.2, 38.8, 37.5, 34.6, 32.1, 31.1, 29.3, 28.4, 24.9, 22.6, 21.8, 18.9

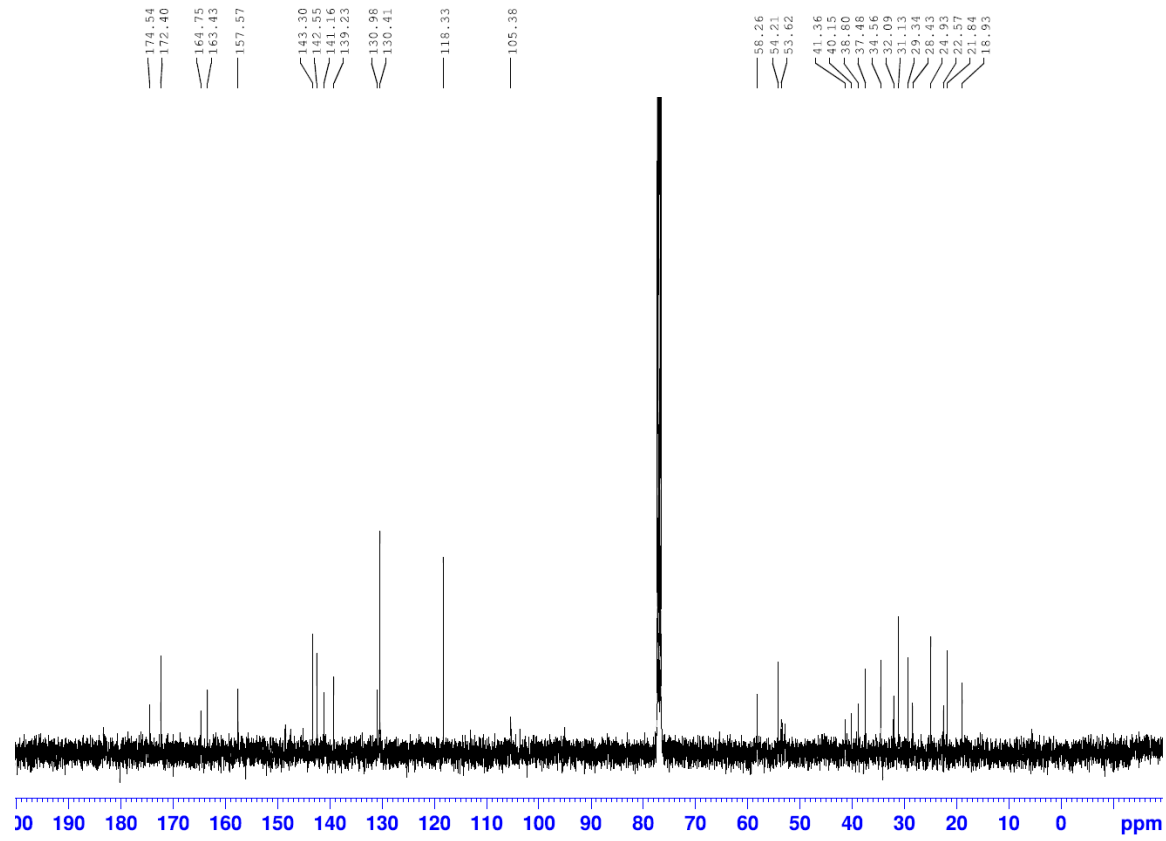
LCMS: $C_{31}H_{40}N_8O_3S$ (M calculated) 604.29, $C_{31}H_{41}N_8O_3S$ (MH^+ found) 605

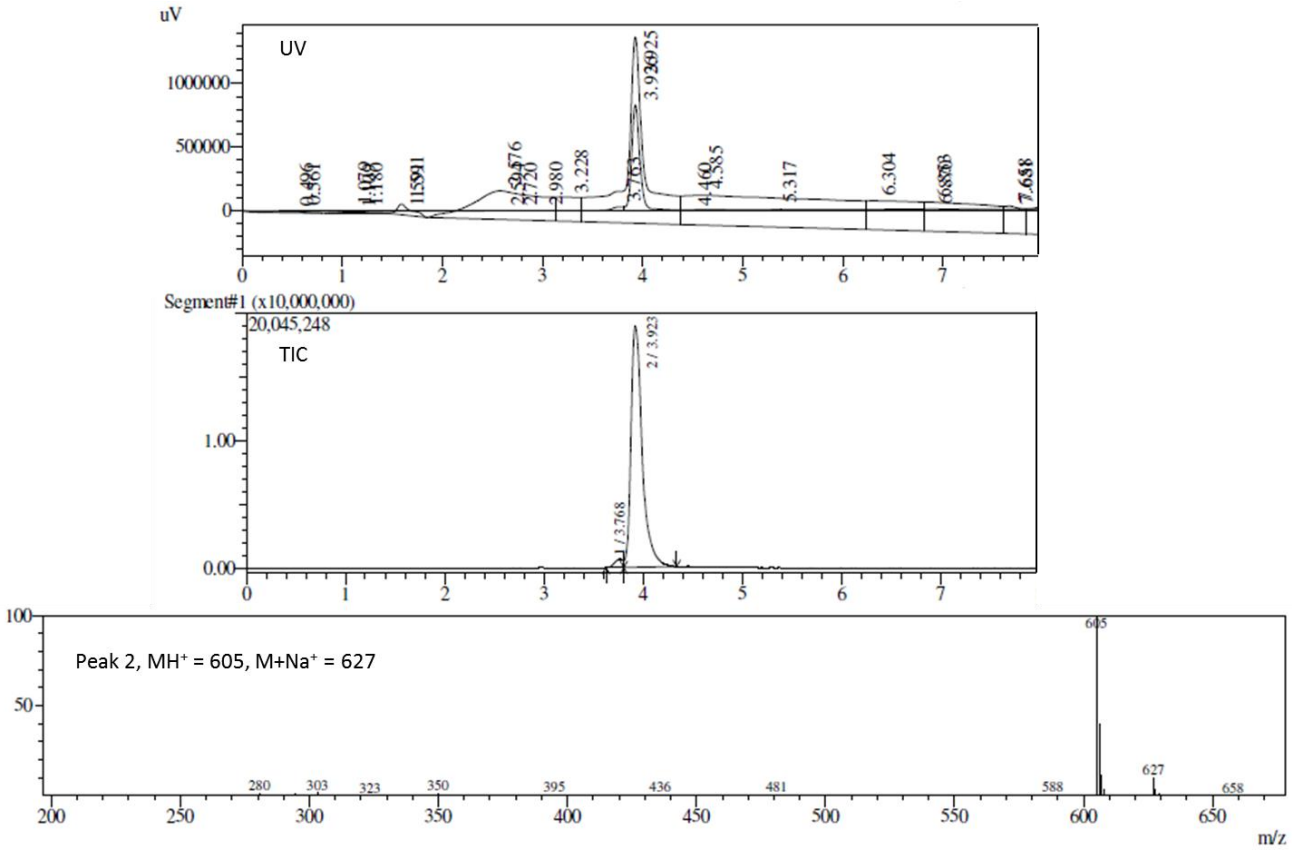
2317 - 15 PURE, 300K, CDCL3

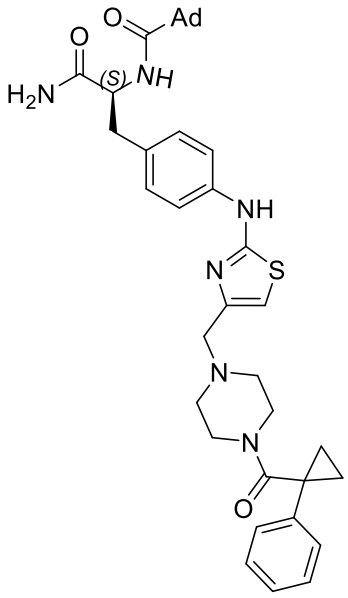


5l

5 PURE, 300K, CDCL3




uV
UV
1000000
500000
0
3.926
3.228
6.304
5.317
0 1 2 3 4 5 6 7
Segment#1 (x10,000,000)
20,045,248
TIC
2 / 3.923
1 / 3.768
1.00
0.00
0 1 2 3 4 5 6 7
100
50
Peak 2, MH+ = 605, M+Na+ = 627
605
627
658
588
481
436
395
350
323
303
280
200 250 300 350 400 450 500 550 600 650
m/z



5m

$C_{38}H_{46}N_6O_3S$

Exact Mass: 666.34

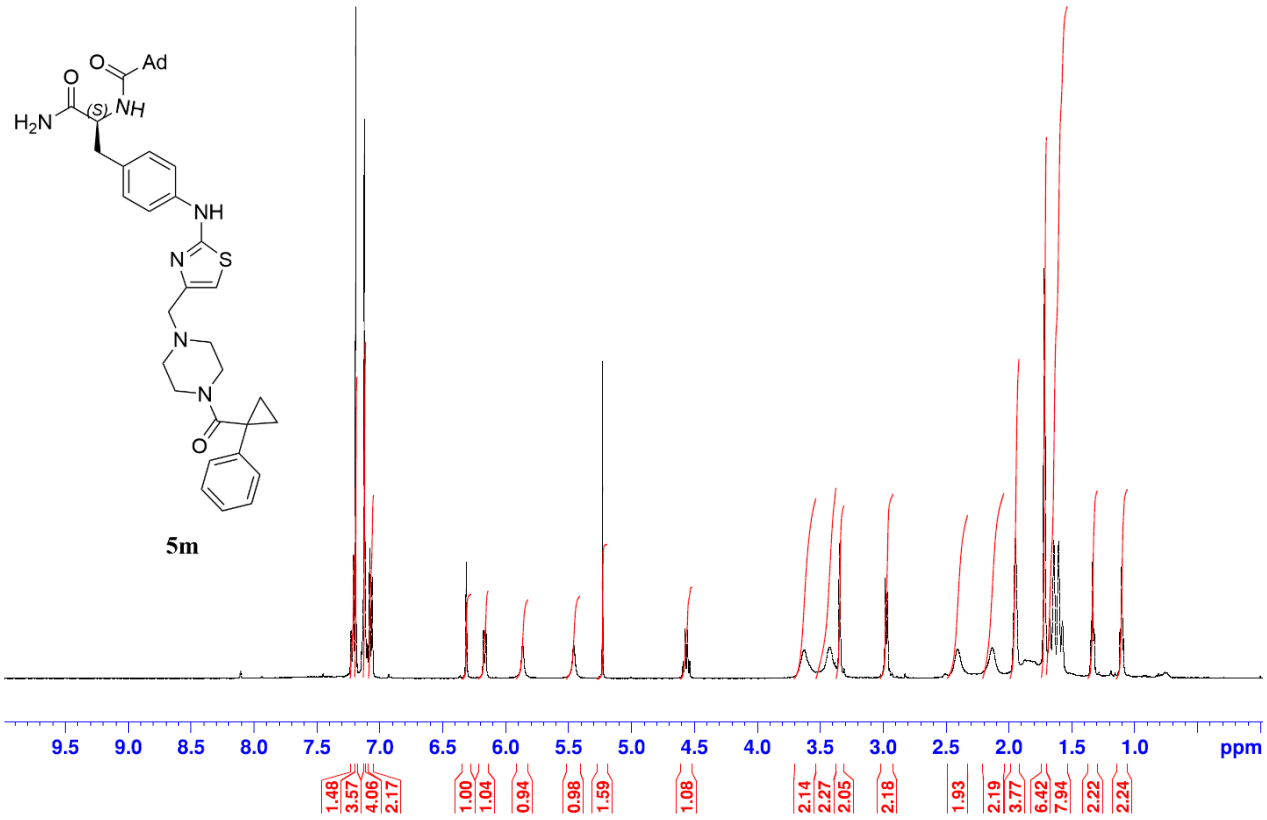
Mol. Wt.: 666.88

5m (^{1}H NMR, 400 MHz, $CDCl_3$, 300 K) δ 7.24 – 7.05 (m, 10H), 6.32 (s, 1H), 6.17 (d, J = 9.1 Hz, 1H), 5.87 (S_{broad}, 1H), 5.46 (s_{broad} , 1H), 5.23 (s, 2H), 4.56 (q, J = 7.5 Hz, 1H), 3.62 (s_{broad}, 2H), 3.43 (s_{broad}, 2H), 3.34 (s, 2H), 2.97 (s, J = 7.1 Hz, 2H), 2.40 ($s_{v.\ broad}$, 2H), 2.13 ($s_{v.\ broad}$, 2H), 1.95 (s_{broad}, 2H), 1.72 (m, 6H), 1.62 (q, J = 15.5 Hz, 8H), 1.35-1.32 (m, 2H), 1.12-1.08 (m, 2H)

5m (^{13}C NMR, 100 MHz, $CDCl_3$, 300 K) δ 178.1, 173.1, 170.9, 164.9, 140.7, 139.2, 131.3, 130.4, 128.7, 126.3, 125.3, 118.4, 105.1

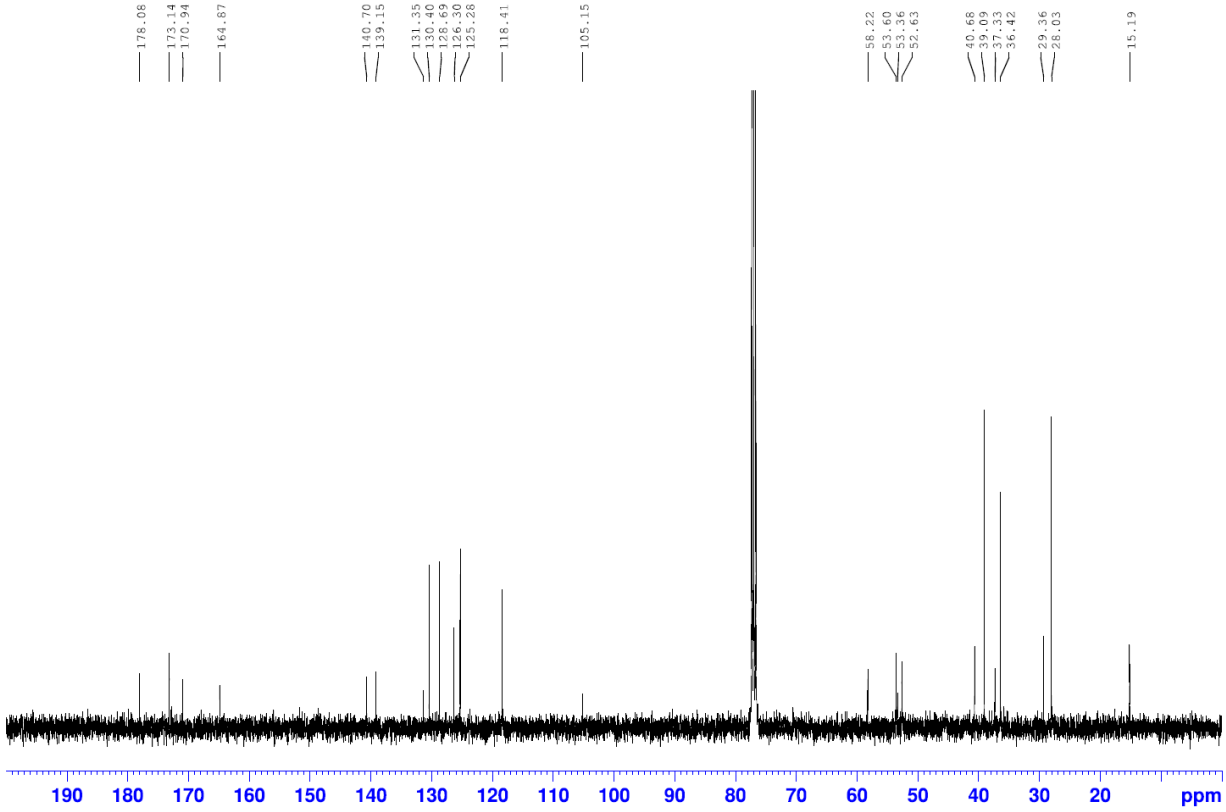
LCMS: $C_{38}H_{46}N_6O_3S$ (M calculated) 666.88, $C_{38}H_{47}N_6O_3S$ (MH^+ found) 667

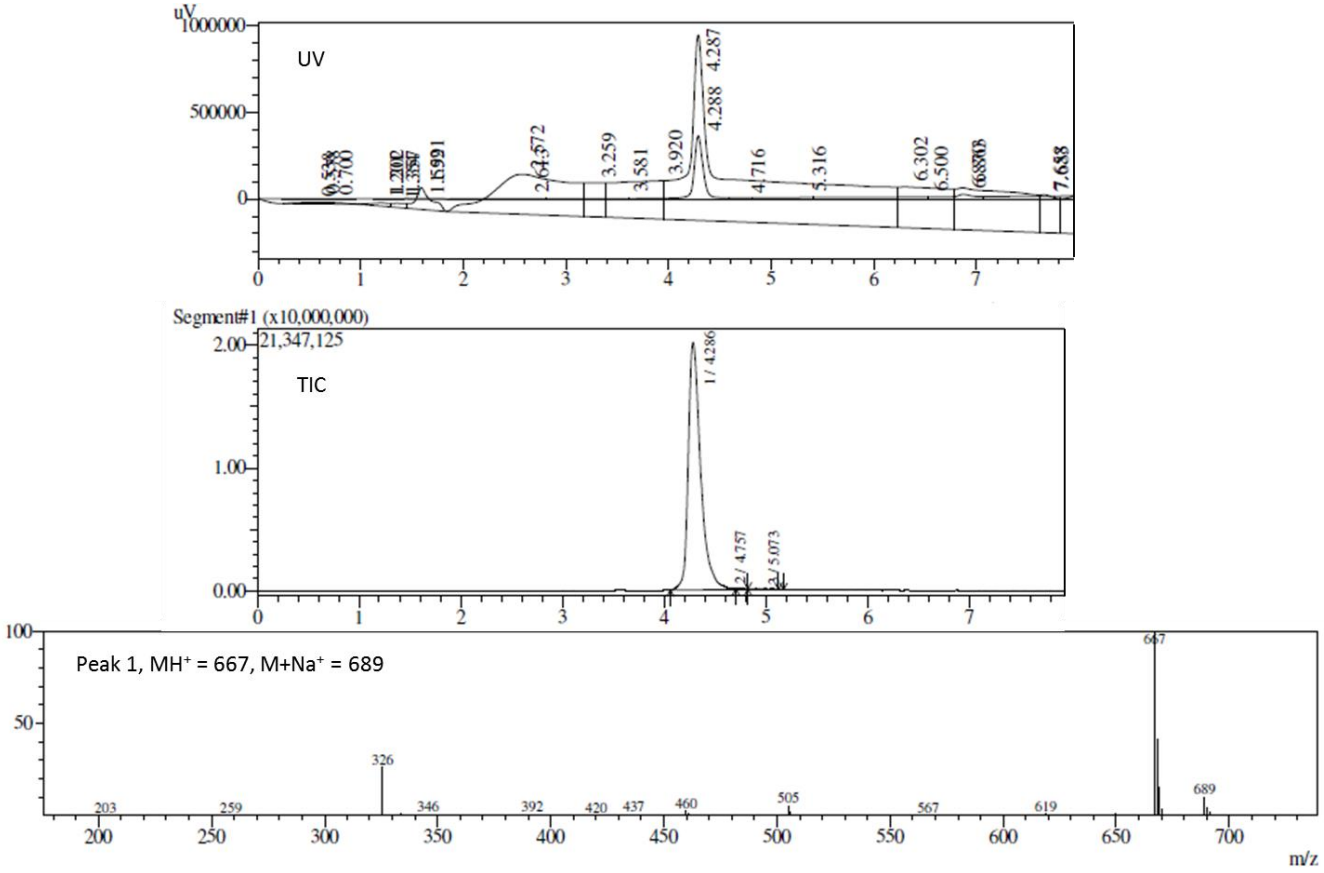
2317 - 16 PURE, 300K, CDCL3

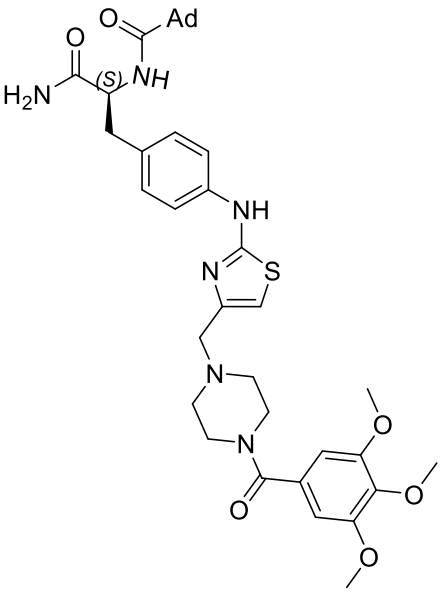


5m

2317 - 16 PURE, 300K, CDCL3




uV
1000000
500000
0
UV
4.287
4.288
3.259
3.581
3.920
4.716
5.316
6.302
6.500
7.688
0 1 2 3 4 5 6 7
Segment#1 (x10,000,000)
2.00
1.00
0.00
21,347,125
TIC
1 / 4.286
2 / 4.757
3 / 5.073
0 1 2 3 4 5 6 7
100
50
Peak 1, MH+ = 667, M+Na+ = 689
667
326
689
203
259
346
392
420
437
460
505
567
619
200 250 300 350 400 450 500 550 600 650 700
m/z



5n

$C_{38}H_{48}N_6O_6S$

Exact Mass: 716.34

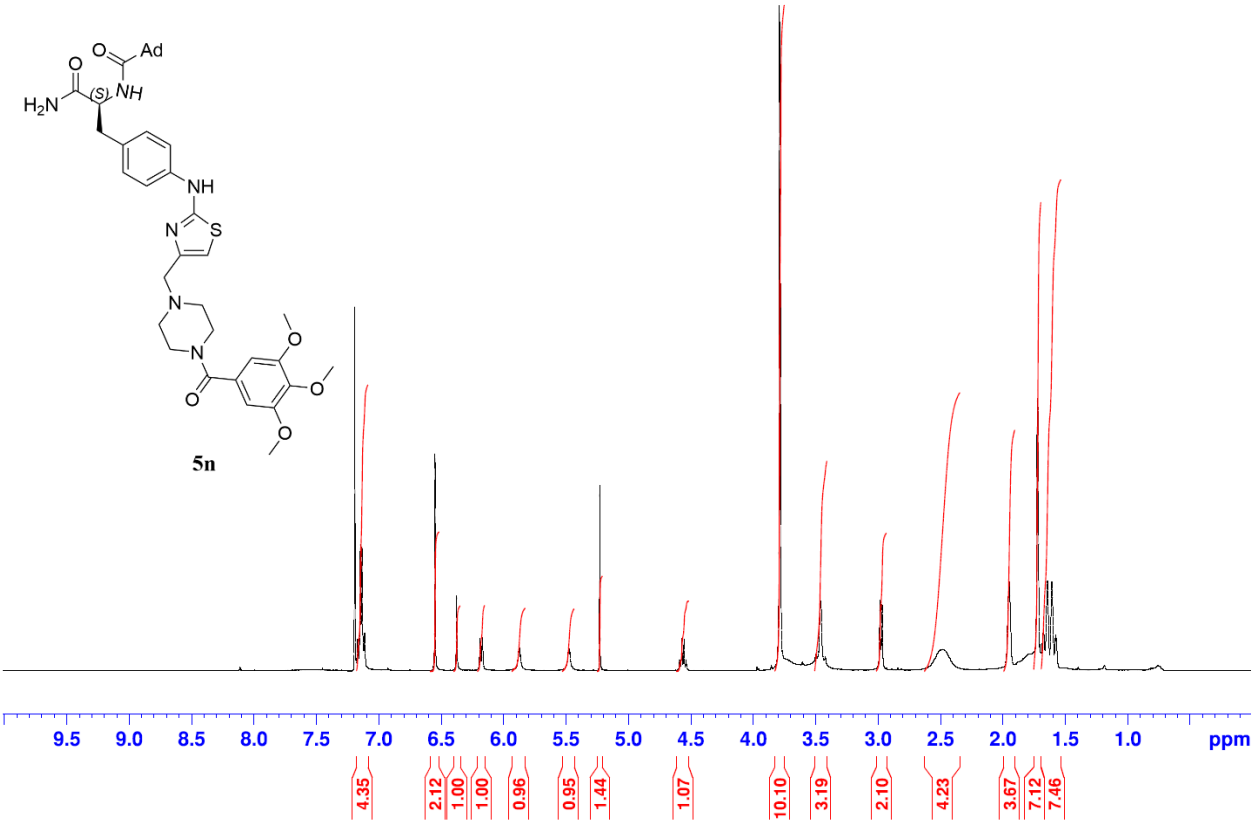
Mol. Wt.: 716.89

5n (^{1}H NMR, 400 MHz, $CDCl_3$, 300 K) δ 7.14 (d, J = 5.5 Hz, 4H), 6.55 (s, 2H), 6.38 (s, 1H), 6.18 (d, J = 7.8 Hz, 1H), 5.87 (s_{broad}, 1H), 5.48 (s_{broad}, 1H), 5.23 (s, 2H), 4.56 (q, J = 7.7 Hz, 1H), 3.79 (s, 9H), 3.78 (s, 2H), 3.46 (d, J = 2.8 Hz, 2H), 2.98 (d, J = 6.7 Hz, 2H), 2.48 ($s_{v.broad}$, 2H), 1.95 (s_{broad}, 2H), 1.72 (s_{broad}, 7H), 1.63 (q, J = 15.8 Hz, 7H)

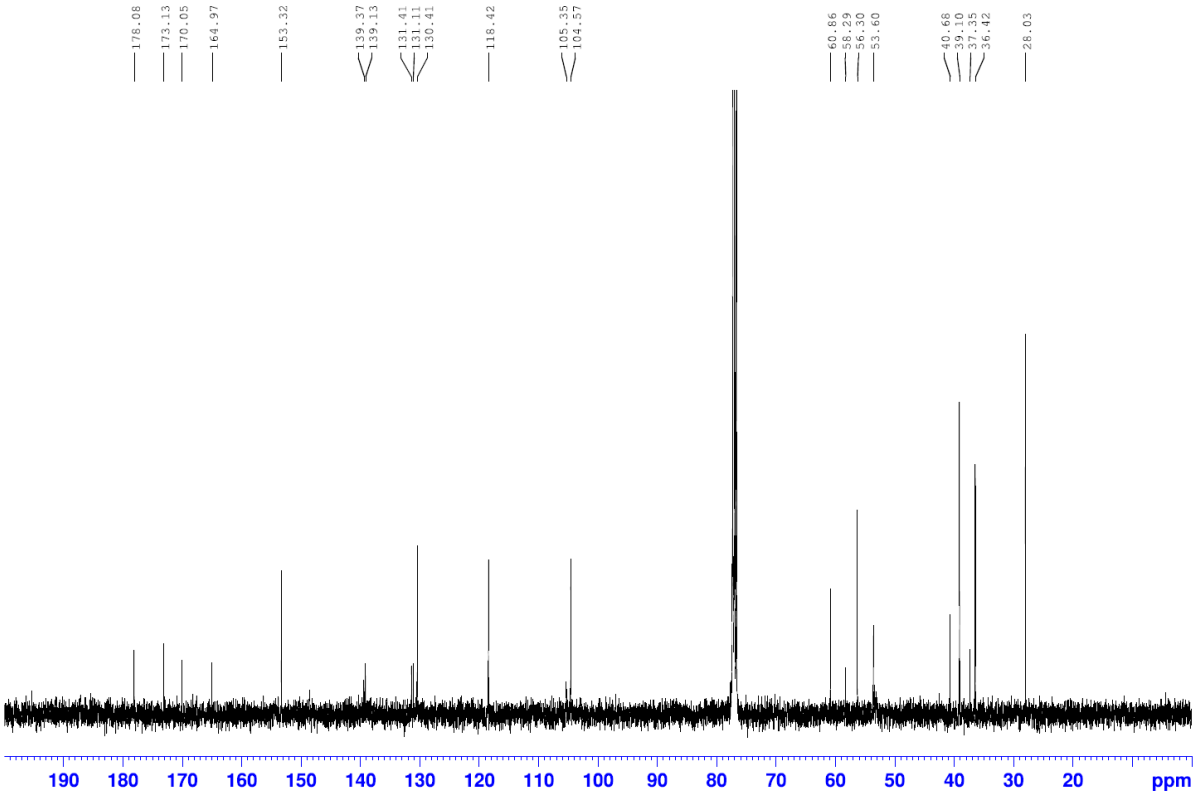
5n (^{13}C NMR, 100 MHz, $CDCl_3$, 300 K) δ 178.1, 173.1, 170.0, 165.0, 153.3, 139.4, 139.1, 131.4, 131.1, 130.4, 118.4, 105.4, 104.6, 60.9, 58.3, 56.3, 53.6, 40.7, 39.1, 37.3, 36.4, 28.0

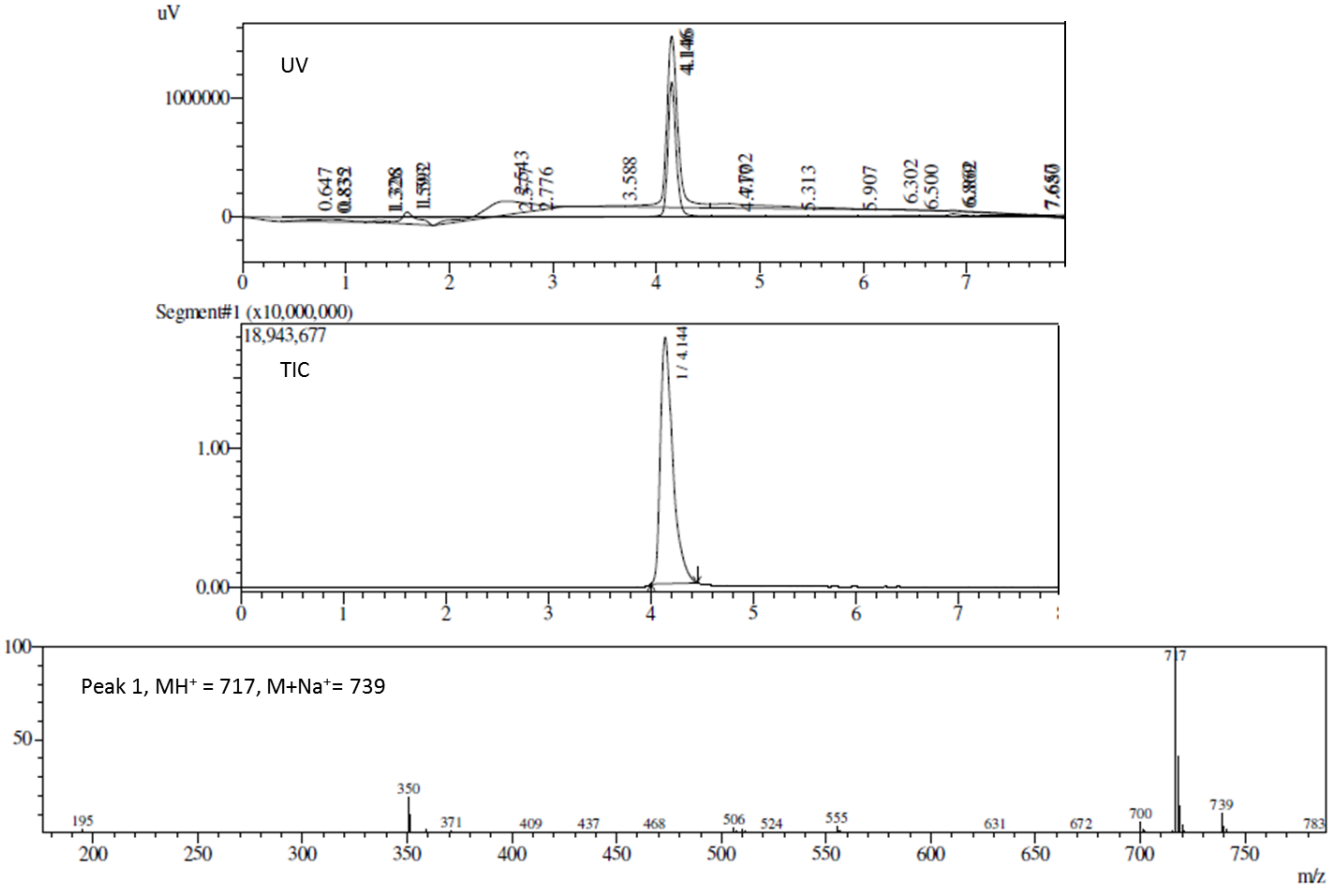
LCMS: $C_{38}H_{48}N_6O_6S$ (M calculated) 716.89, $C_{38}H_{48}N_6O_6S$ (MH^+ found) 717

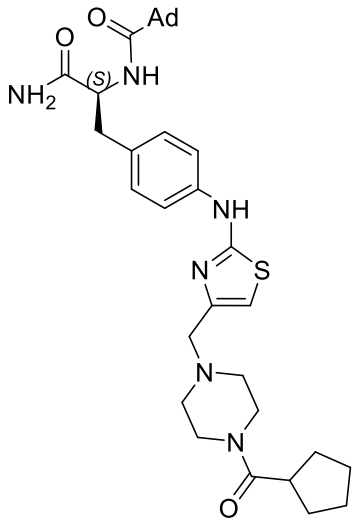
2317 - 18 PURE, 300K, CDCL3



2317 - 18 PURE, 300K, CDCL3




uV
UV
1000000
0
0.647
0.832
1.326
1.592
2.776
3.588
4.144
5.313
5.907
6.302
6.500
7.650
0
1
2
3
4
5
6
7
Segment#1 (x10,000,000)
18,943,677
TIC
1.00
0.00
1 / 4.144
100
50
Peak 1, MH+ = 717, M+Na+= 739
717
350
195
371
409
437
468
506
524
555
631
672
700
739
783
200
250
300
350
400
450
500
550
600
650
700
750
m/z



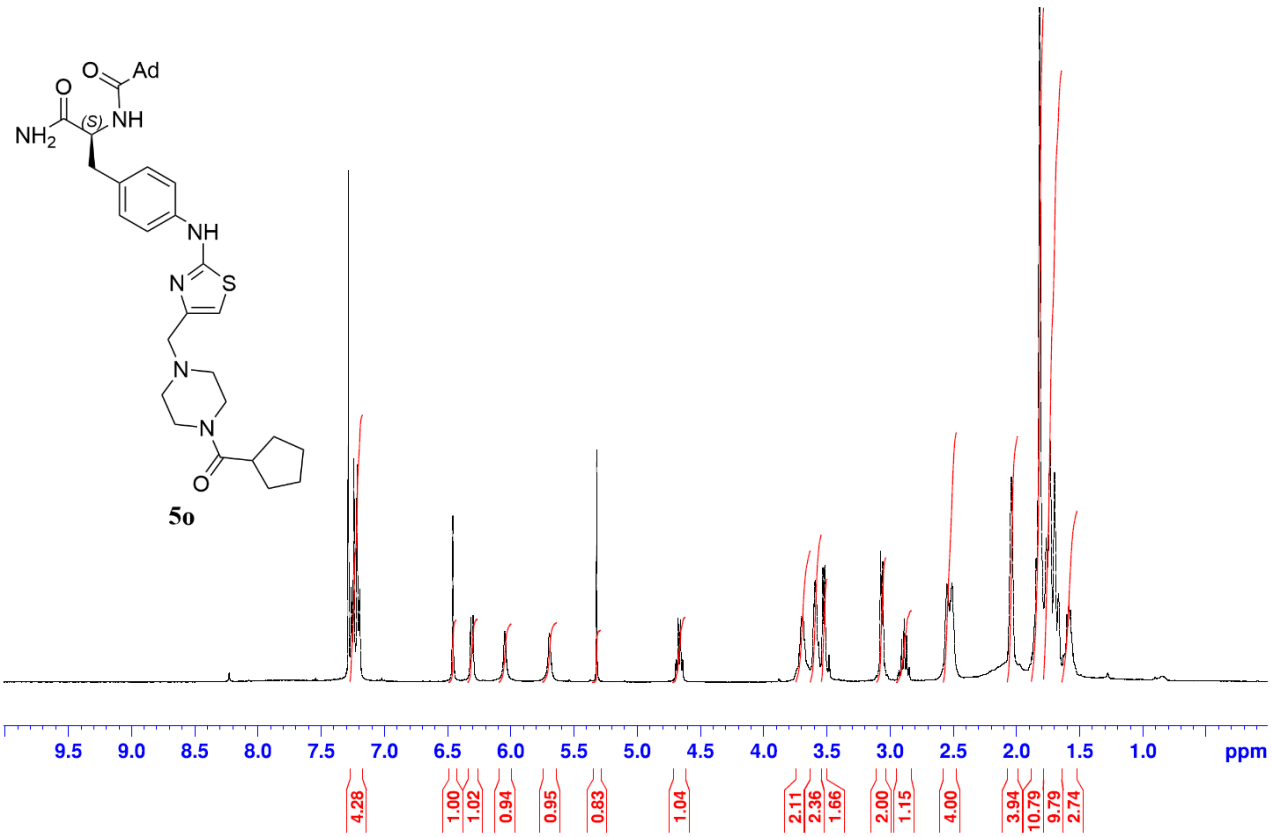
5o
$C_{34}H_{46}N_6O_3S$
Exact Mass: 618.34
Mol. Wt.: 618.83

5o (¹H NMR, 400 MHz, $CDCl_3$, 300 K) δ 7.23 (q, J = 10.6 Hz, 4H), 6.46 (s, 1H), 6.31 (d, J = 8.7 Hz, 1H), 6.05 (s_{broad}, 1H), 5.69 (s_{broad}, 1H), 5.32 (s, 1H), 4.67 (q, J = 6.7 Hz, 1H), 3.76 – 3.65 (m, 2H), 3.62-3.56 (m, 2H), 3.53 (d, J = 6.7 Hz, 2H), 3.01 (d, J = 6.3 Hz, 2H), 2.89 (pent. J = 7.9 Hz, 1H), 2.55 (s_{broad}, 2H), 2.51 (s_{broad}, 2H), 2.04 (s_{broad}, 4H), 1.82 (s, 9H), 1.72 (q, J = 14.1 Hz, 9H), 1.60 – 1.50 (m, 2H)

5o (¹³C NMR, 100 MHz, $CDCl_3$, 300 K) δ 178.1, 174.5, 173.2, 165.0, 139.2, 131.3, 130.4, 118.4, 105.3, 58.3, 53.6, 53.5, 52.9, 45.3, 41.6, 41.0, 40.7, 39.1, 37.4, 36.4, 30.1, 28.0, 26.0

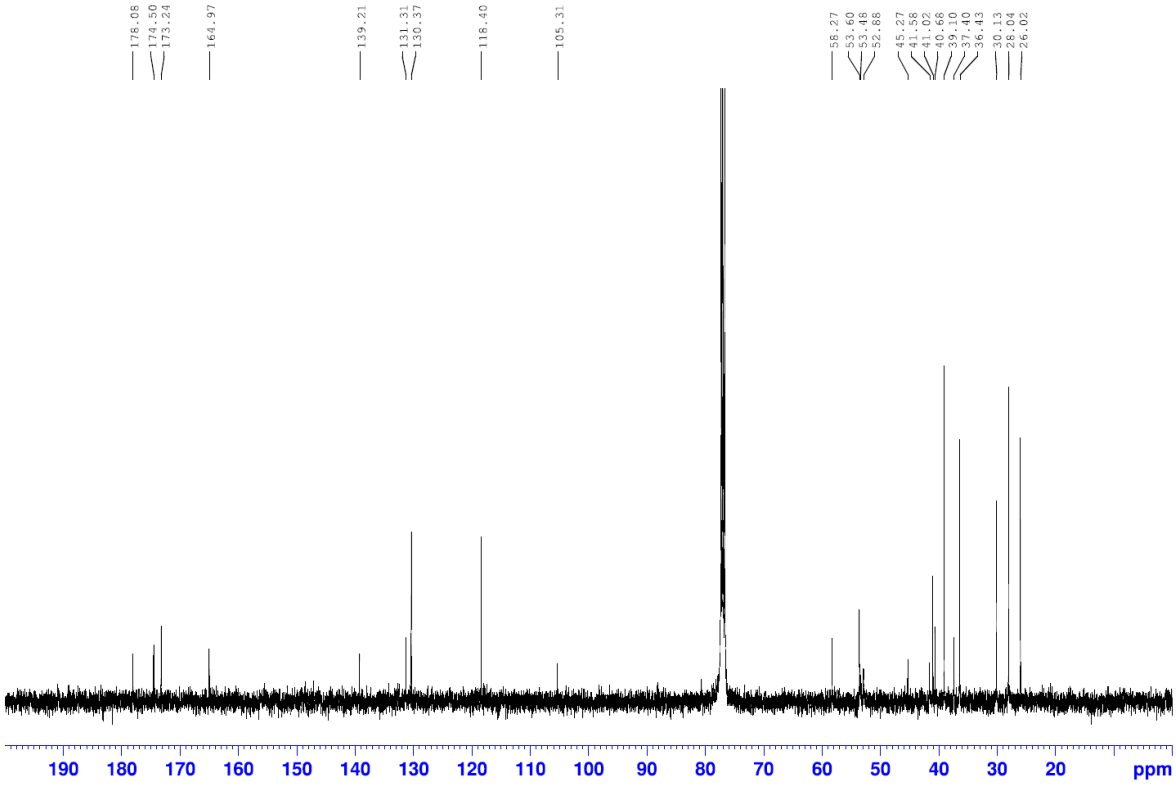
LCMS: $C_{34}H_{46}N_6O_3S$ (M calculated) 618.83, $C_{34}H_{47}N_6O_3S$ (MH^+ found) 619

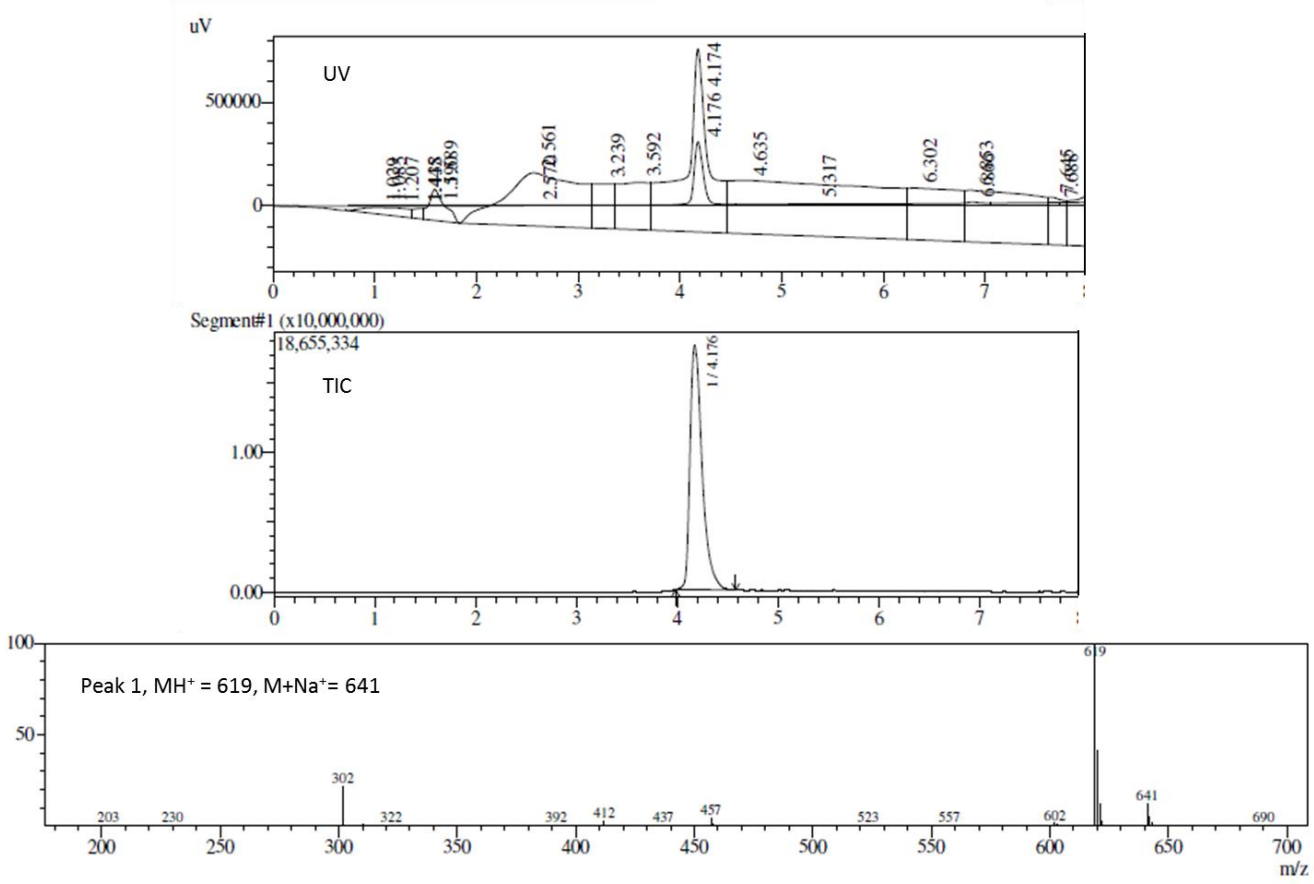
2317 - 19 PURE, 300K, CDCL3

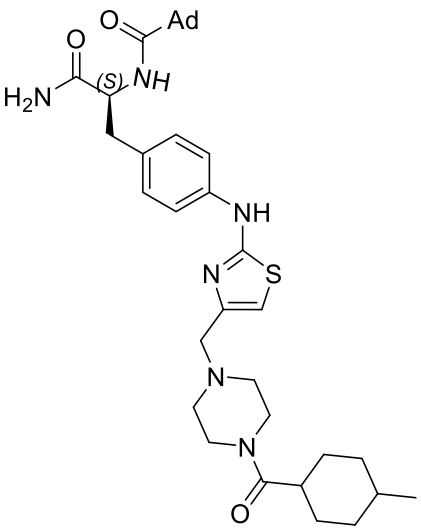


5o

2317 - 19 PURE, 300K, CDCL3




uV
UV
500000
0
4.176 4.174
3.239
3.592
4.635
5.317
6.302
Segment#1 (x10,000,000)
18,655,334
TIC
1.00
0.00
1/ 4.176
Peak 1, MH+ = 619, M+Na+= 641
100
50
619
302
641
203
230
322
392
412
437
457
523
557
602
690
m/z



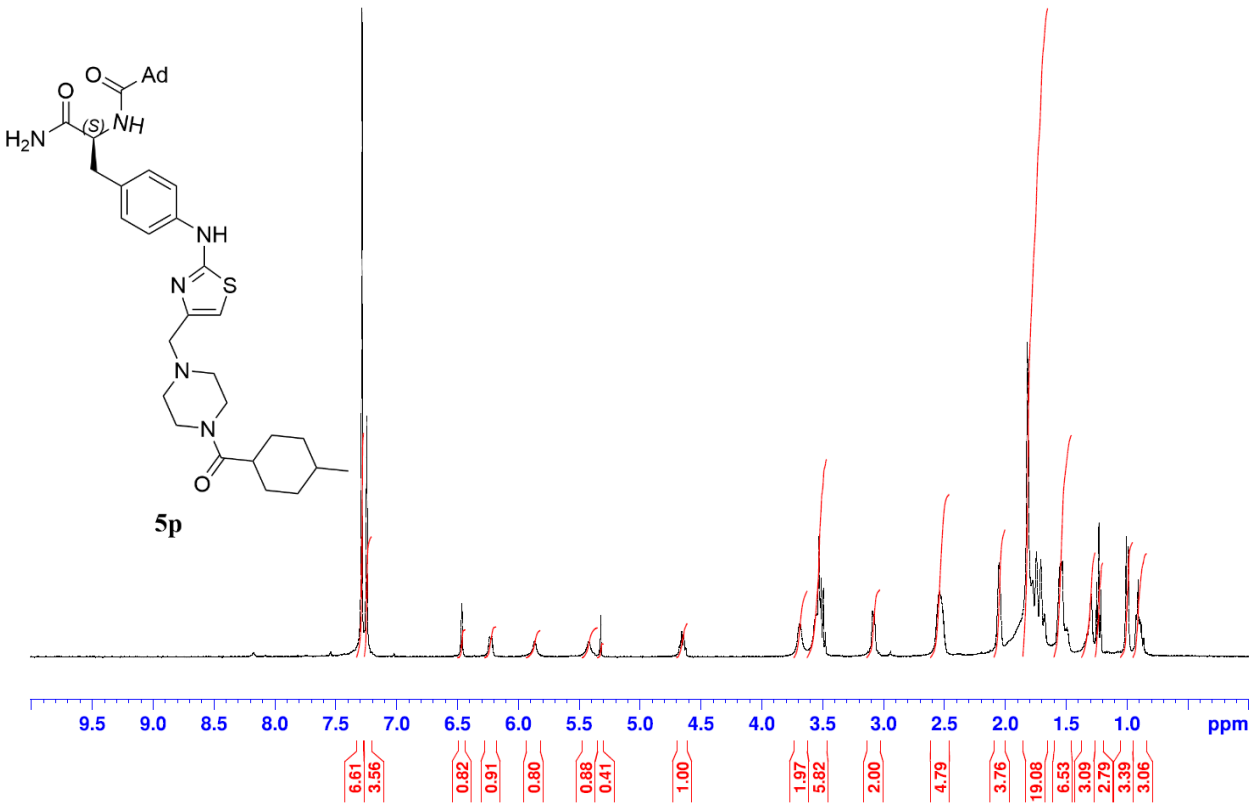
5p
$C_{36}H_{50}N_6O_3S$
Exact Mass: 646.37
Mol. Wt.: 646.89

5p (^{1}H NMR, 400 MHz, $CDCl_3$, 300 K) δ 7.27 (d, J = 15.5 Hz, 4H), 6.46 (s, 1H), 6.23 (d, J = 8.4 Hz, 1H), 5.87 (s_{broad}, 1H), 5.42 (s_{broad}, 1H), 4.65 (q, J = 8.4 Hz, 1H), 3.68 (s_{broad}, 2H), 3.56 (s_{broad}, 2H), 3.52 (pent., J = 6.9 Hz, 1H), 3.13-3.1 (m, 2H), 2.54 (s_{broad}, 4H), 2.05 (s, 4H), 1.82 (s, 9H), 1.73 (q, J = 14.7 Hz, 6H), 1.58 – 1.47 (m, 6H), 1.30 (s, 2H), 1.23 (t, J = 7.3 Hz, 2H), 1.0 (d, J = 5.5 Hz, 3H), 0.94-0.86 (m, 3H)

5p (^{13}C NMR, 100 MHz, $CDCl_3$, 300 K) δ 178.1, 173.1, 139.1, 131.4, 130.4, 118.5, 105.3, 65.8, 58.3, 53.6, 40.7, 39.1, 38.8, 37.3, 36.4, 31.6, 31.1, 28.4, 28.0, 24.9, 22.6, 18.9, 15.2, 14.1

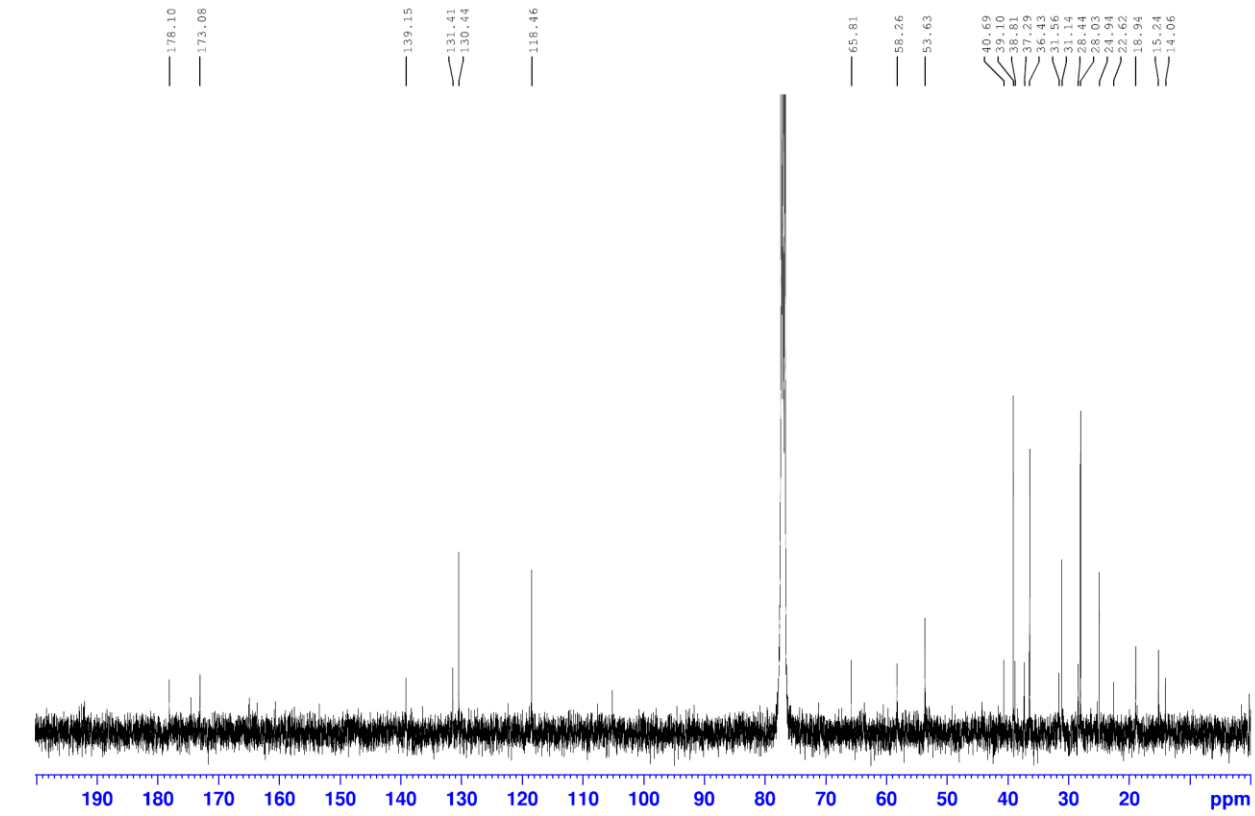
LCMS: $C_{36}H_{50}N_6O_3S$ (M calculated) 646.89, $C_{36}H_{51}N_6O_3S$ (MH^+ found) 647

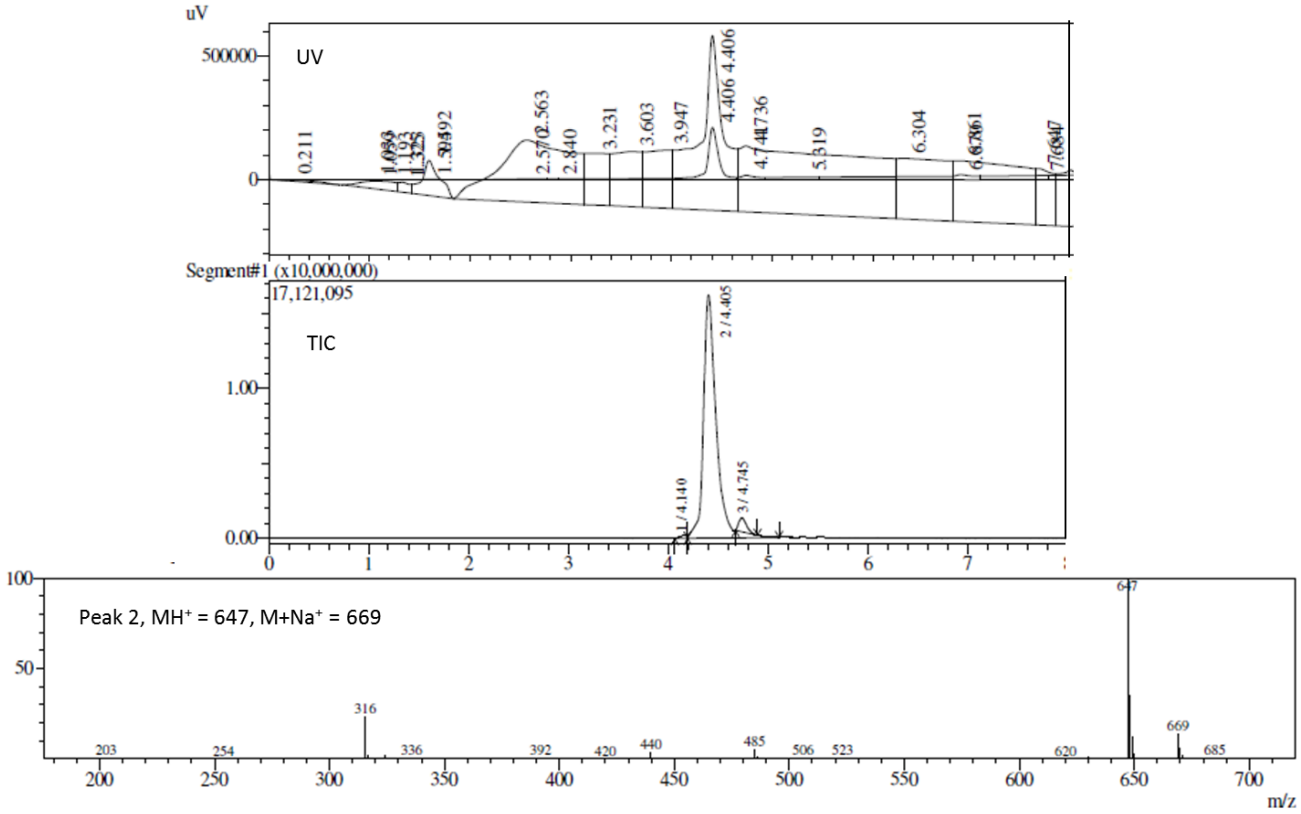
2317 - 20 PURE, 300K, CDCL3

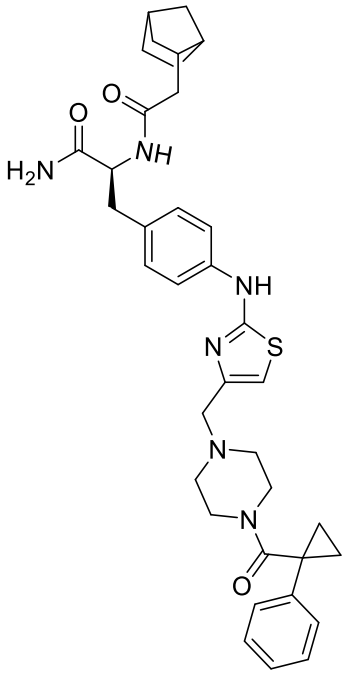


5p

2317 - 20 PURE, 300K, CDCL3




uV
500000
UV
0
0.211
2.563
2.840
3.231
3.603
3.947
4.406
4.736
5.319
6.304
Segment#1 (x10,000,000)
17,121,095
TIC
1.00
0.00
2 / 4.405
1 / 4.140
3 / 4.745
0
1
2
3
4
5
6
7
100
50
Peak 2, MH+ = 647, M+Na+ = 669
647
316
669
203
254
336
392
420
440
485
506
523
620
685
200
250
300
350
400
450
500
550
600
650
700
m/z



5q

$C_{36}H_{44}N_6O_3S$

Exact Mass: 640.32

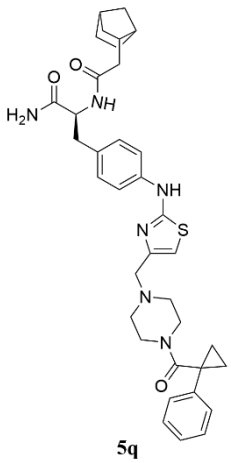
Mol. Wt.: 640.84

5q (¹H NMR, 400 MHz, $CDCl_3$, 300 K) δ 7.31 (d, J = 7.5 Hz, 2H), 7.24 – 7.20 (m, 5H), 7.16 (d, J = 7.3 Hz, 2H), 6.41 (s, 1H), 6.17 (d, J = 7.2 Hz, 1H), 5.96 (s_{broad}, 1H), 5.60 (s_{broad}, 1H), 4.69 (q, J = 7.2 Hz, 1H), 3.72 (s_{broad}, 2H), 3.50 (q, J = 7.7 Hz, 4H), 3.44 (s, 2H), 3.07 (d, J = 8.3 Hz, 2H), 2.50 (s_{broad}, 2H), 2.51 (s_{broad}, 2H), 2.16 (dd, J_{AB} = 7.0 Hz, J_{BC} = 7.6 Hz, 1H), 2.03 (dd, J_{AB} = 8.7 Hz, J_{BC} = 6.5 Hz, 1H), 1.89 – 1.80 (m, 2H), 1.49-1.40 (m, 5H), 1.33 – 1.26 (m, 3H), 1.23 (t, J = 7.2 Hz, 4H), 1.21 – 1.16 (m, 3H), 1.15 – 1.06 (m, 3H), 1.06 – 0.98 (m, 2H), 0.93 – 0.86 (m 3H)

5q (¹³C NMR, 100 MHz, $CDCl_3$, 300 K) δ 173.0, 172.6, 171.0, 164.8, 140.7, 139.1, 131.2, 130.3, 128.7, 126.3, 125.3, 118.3, 65.8, 58.1, 53.8, 52.6, 43.5, 41.0, 38.9, 37.7, 37.4, 36.7, 35.2, 31.6, 29.8, 29.4, 28.5, 22.6, 15.2, 15.2, 14.1

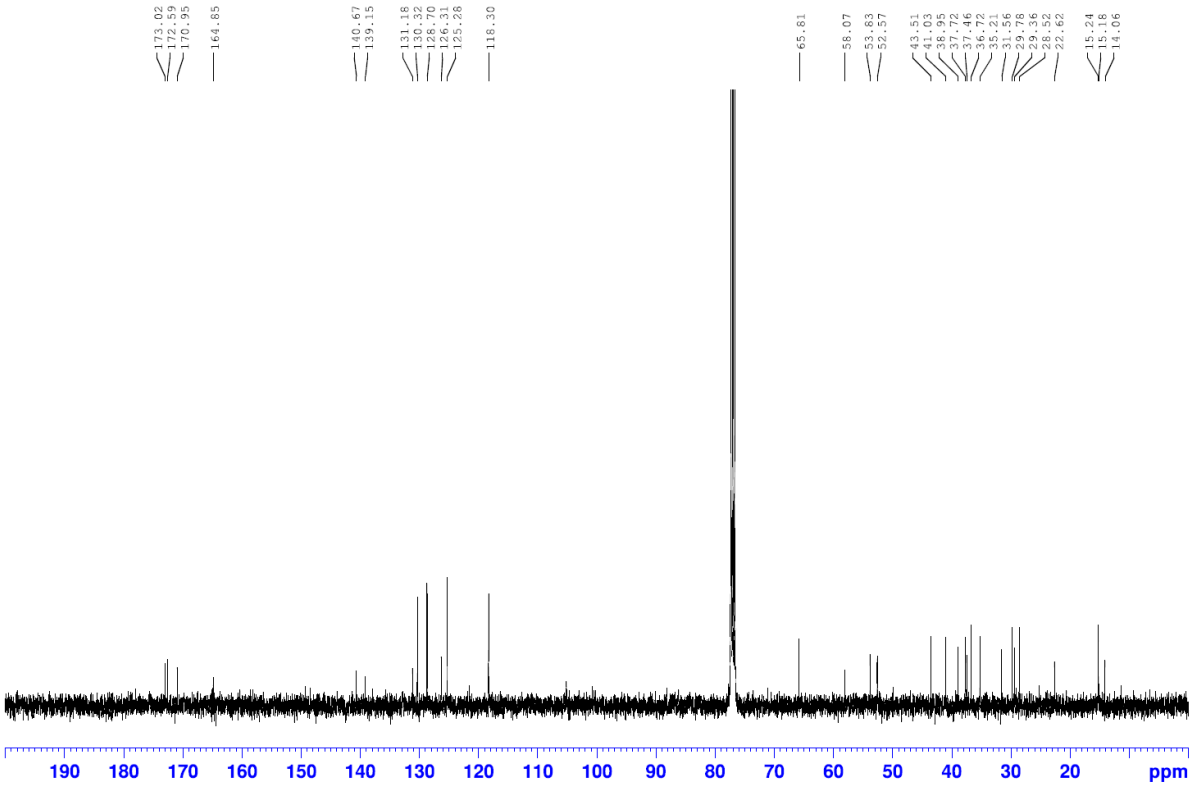
LCMS: $C_{36}H_{44}N_6O_3S$ (M calculated) 640.84, $C_{36}H_{45}N_6O_3S$ (MH^+ found) 641

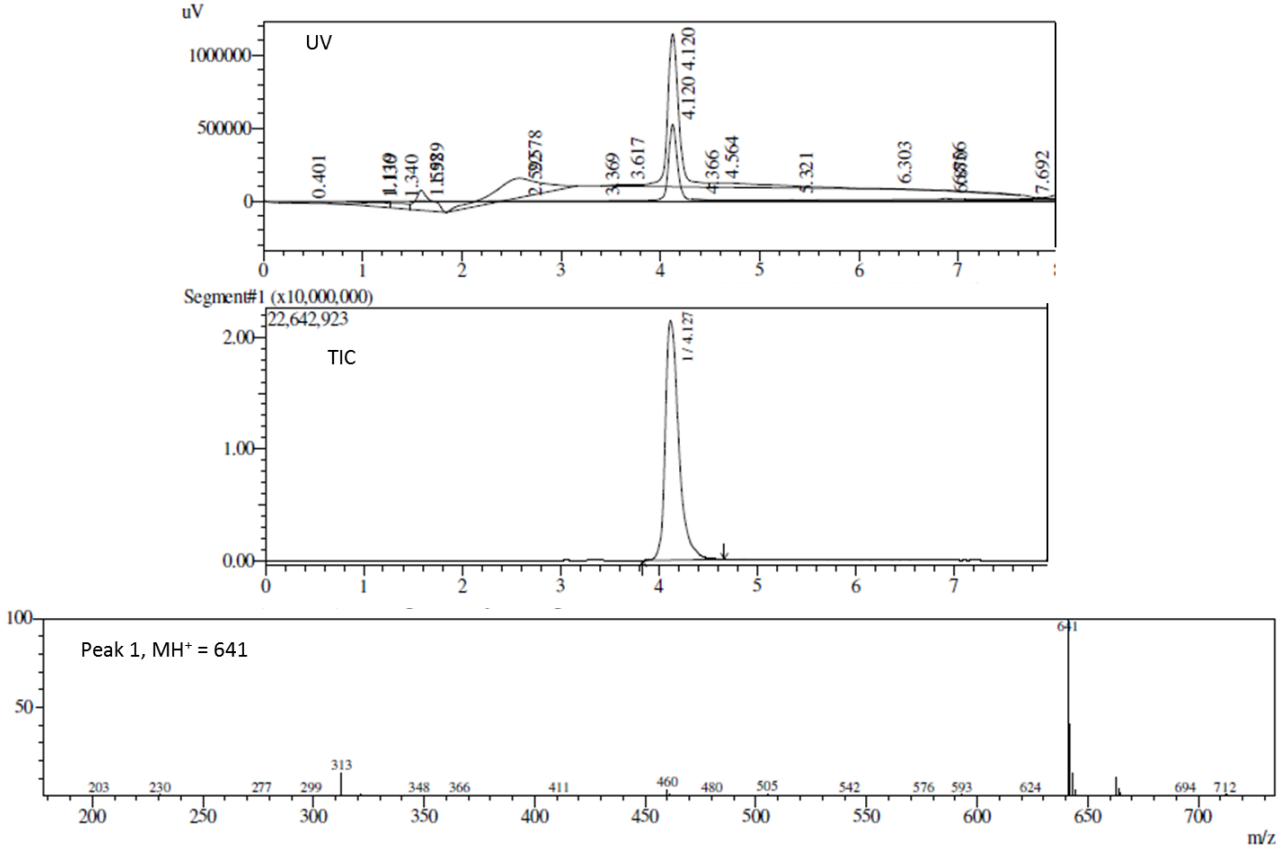
2317 - 21 PURE, 300K, CDCL3

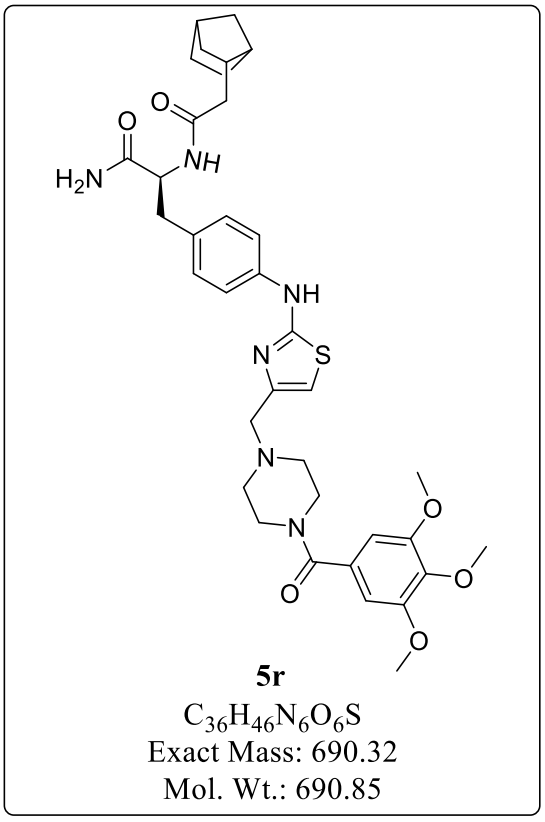


5q

2317 - 21 PURE, 300K, CDCL3




uV
UV
1000000
500000
0
0.401
1.340
3.369
3.617
4.120
4.366
4.564
5.321
6.303
7.692
0 1 2 3 4 5 6 7
Segment#1 (x10,000,000)
22,642,923
TIC
2.00
1.00
0.00
4.127
0 1 2 3 4 5 6 7
100
50
Peak 1, MH+ = 641
641
313
203 230 277 299 348 366 411 460 480 505 542 576 593 624 694 712
200 250 300 350 400 450 500 550 600 650 700
m/z



5r

$C_{36}H_{46}N_6O_6S$

Exact Mass: 690.32

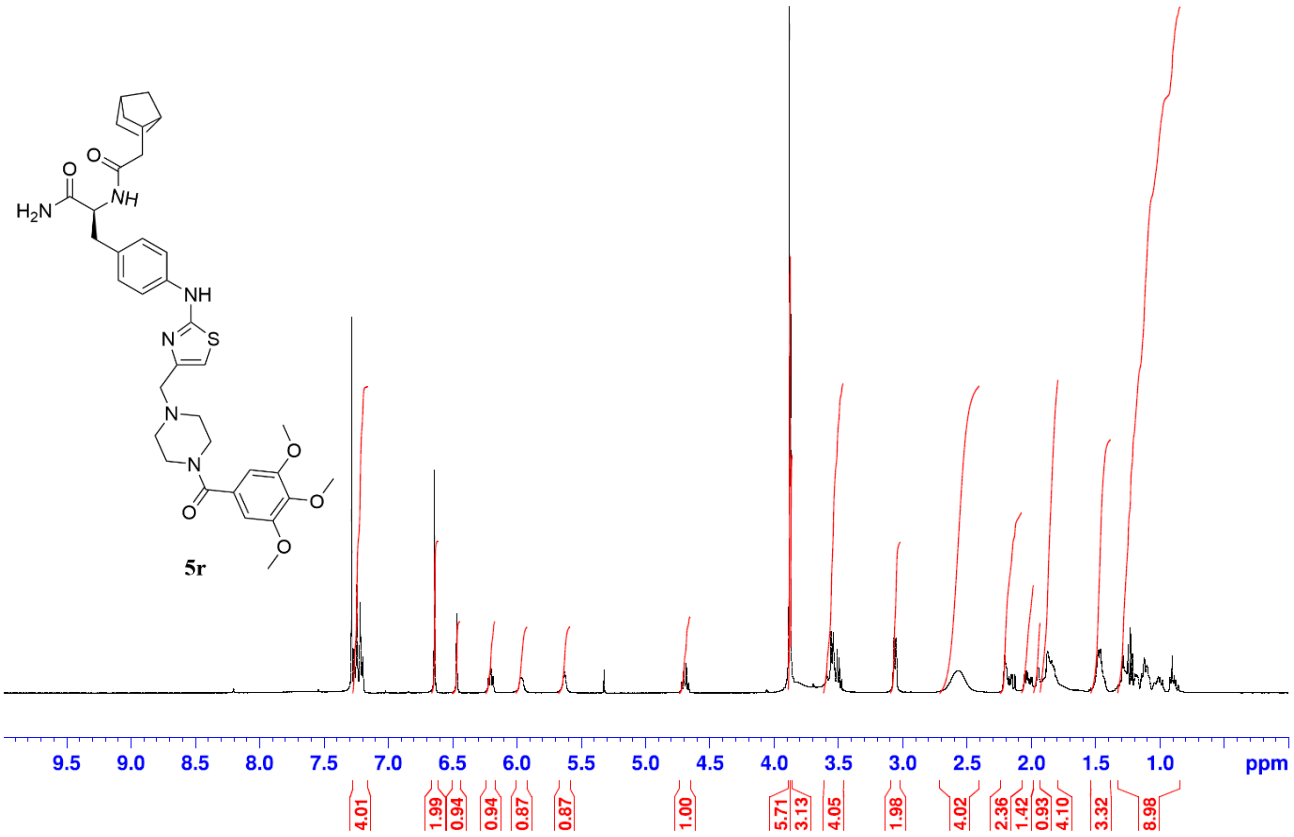
Mol. Wt.: 690.85

5r (^{1}H NMR, 400 MHz, $CDCl_3$, 300 K) δ 7.23 (d, J = 9.2 Hz, 4H), 6.64 (s, 2H), 6.47 (s, 1H), 6.20 (t, J = 7.4 Hz, 1H), 5.97 (s_{broad}, 1H), 5.63 (s_{broad}, 1H), 4.69 (q, J = 8.0 Hz, 1H), 3.88 (s, 9H), 3.87 (s, 2H), 3.55 (q, J = 7.5 Hz, 3H), 3.50 (Q, J = 7.0 Hz, 1H), 3.06 (d, J = 8.0 Hz, 2H), 2.57 ($s_{v.broad}$, 4H), 2.24 – 2.18 (m, 1H), 2.16 (dd, J_{AB} = 4.2 Hz, J_{BC} = 3.8 Hz, 1H), 2.13 (s, 1H), 2.04 (dd, J_{AB} = 3.4 Hz, J_{BC} = 4.2 Hz, 1H), 1.95 (s,1H), 1.90 – 1.80 (m, 4H), 1.51 – 1.42 (m, 3H), 1.33 – 1.26 (m, 2H), 1.23 (t, J = 7.2 Hz, 3H), 1.20 – 0.97 (m, 6H), 0.93 – 0.86 (m, 1H)

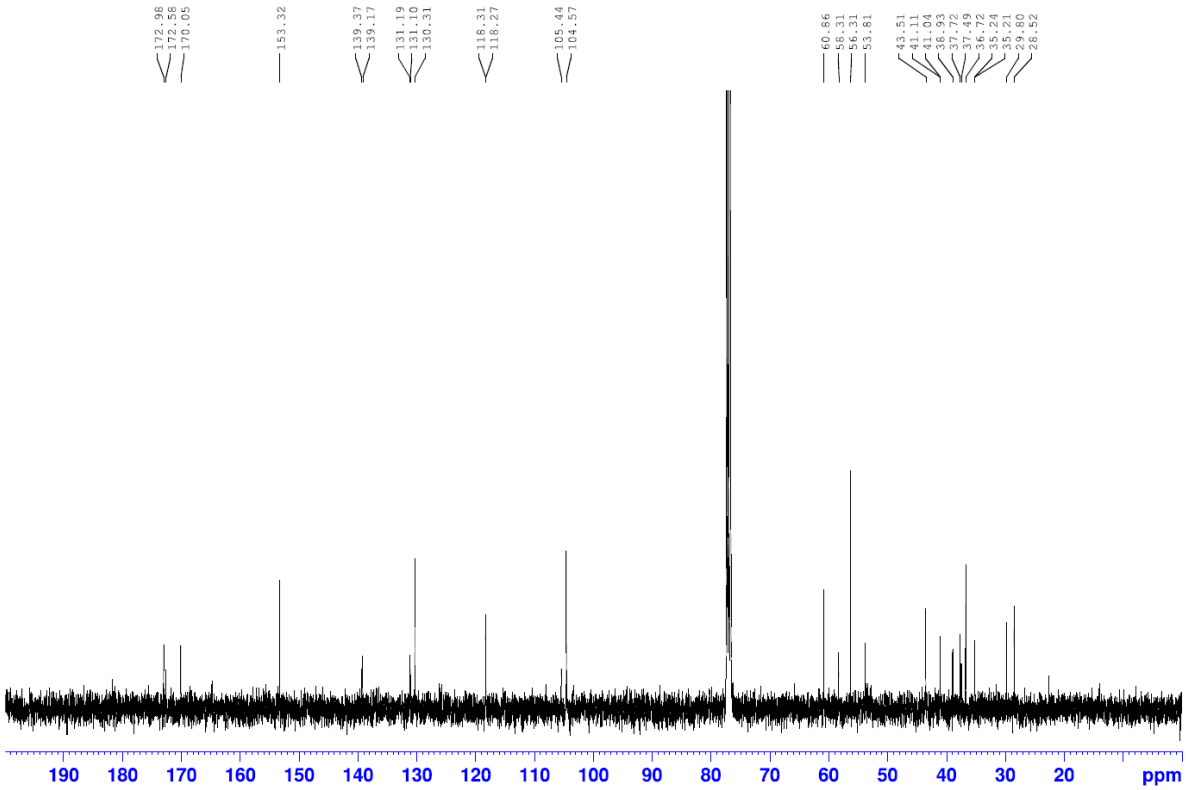
5r (^{13}C NMR, 100 MHz, $CDCl_3$, 300 K) δ 173.0, 172.6, 170.1, 153.3, 139.4, 139.2, 131.2, 131.1, 130.3, 118.3, 118.2, 105.4, 104.6, 60.9, 58.3, 56.3, 53.8, 43.5, 41.1, 41.0, 38.9, 37.7, 37.5, 36.7, 35.2, 35.2, 29.8, 28.5

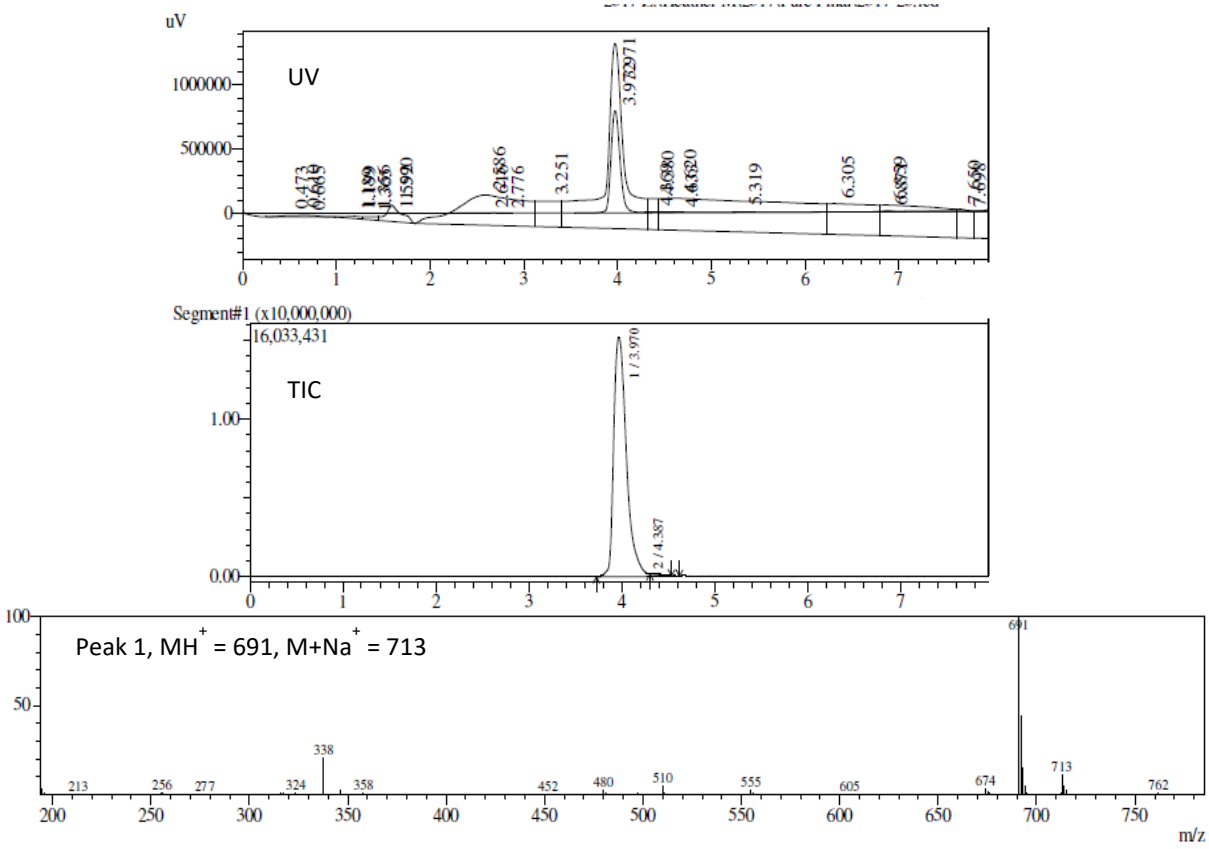
LCMS: $C_{36}H_{46}N_6O_6S$ (M calculated) 690.85, $C_{36}H_{47}N_6O_6S$ (MH^+ found) 691

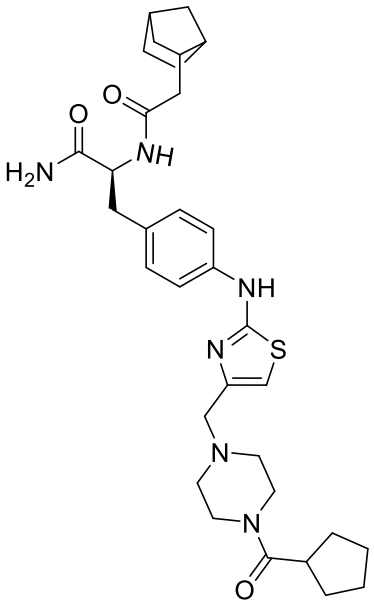
2317 - 23 PURE, 300K, CDCL3



2317 - 23 PURE, 300K, CDCL3




uV
UV
1000000
500000
0
3.972
3.251
5.319
6.305
0 1 2 3 4 5 6 7
Segment#1 (x10,000,000)
16,033,431
TIC
1.00
0.00
1 / 3.970
2 / 4.387
0 1 2 3 4 5 6 7
100
50
Peak 1, MH+ = 691, M+Na+ = 713
691
338
213
256
277
324
358
452
480
510
555
605
674
713
762
200 250 300 350 400 450 500 550 600 650 700 750
m/z



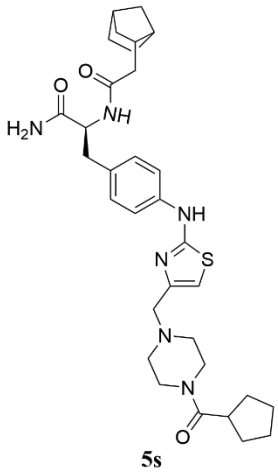
5s
$C_{32}H_{44}N_6O_3S$
Exact Mass: 592.32
Mol. Wt.: 592.80

5s (^{1}H NMR, 400 MHz, $CDCl_3$, 300 K) δ 7.24 (q, J = 7.2 Hz, 4H), 6.46 (s, 1H), 6.17 (t, J = 7.7 Hz, 1H), 5.91 (s_{broad}, 1H), 5.56 (s_{broad}, 1H), 4.69 (q, J = 7.3 Hz, 1H), 3.73 – 3.66 (m, 2H), 3.62 – 3.55 (m, 2H), 3.54 – 3.78 (m, 3H), 3.10 – 3.05 (m, 2H), 2.90 (pent J = 7.9 Hz, 1H), 2.58 – 2.47 (m, 4H), 2.24 – 2.13 (m, 2H), 2.07 – 1.99 (m, 1H), 1.95 (s_{broad}, 1H), 1.90 – 1.70 (m, 13H), 1.65 – 1.54 (m, 2H), 1.52 – 1.42 (m, 4H), 1.34 – 1.07 (m, 8H), 0.94 – 0.86 (m, 1H)

5s (^{13}C NMR, 100 MHz, $CDCl_3$, 300 K) δ 174.5, 173.0, 139.2, 131.1, 130.3, 118.3, 105.2, 75.0, 65.8, 58.4, 53.8, 53.5, 52.9, 45.4, 43.5, 41.7, 41.1, 41.0, 38.9, 37.7, 37.5, 36.7, 35.2, 31.5, 30.8, 30.1, 29.8, 28.5, 26.0, 15.2, 14.0

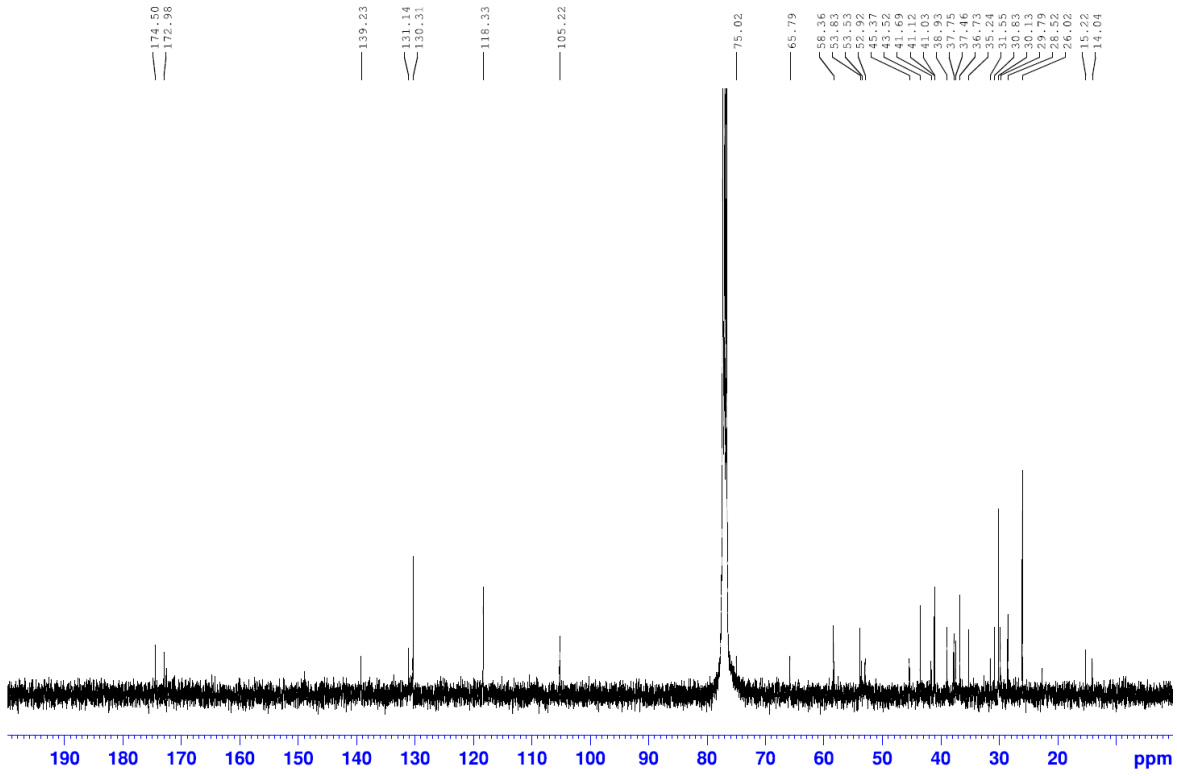
LCMS: $C_{32}H_{44}N_6O_3S$ (M calculated) 592.80, $C_{32}H_{45}N_6O_3S$ (MH^+ found) 593

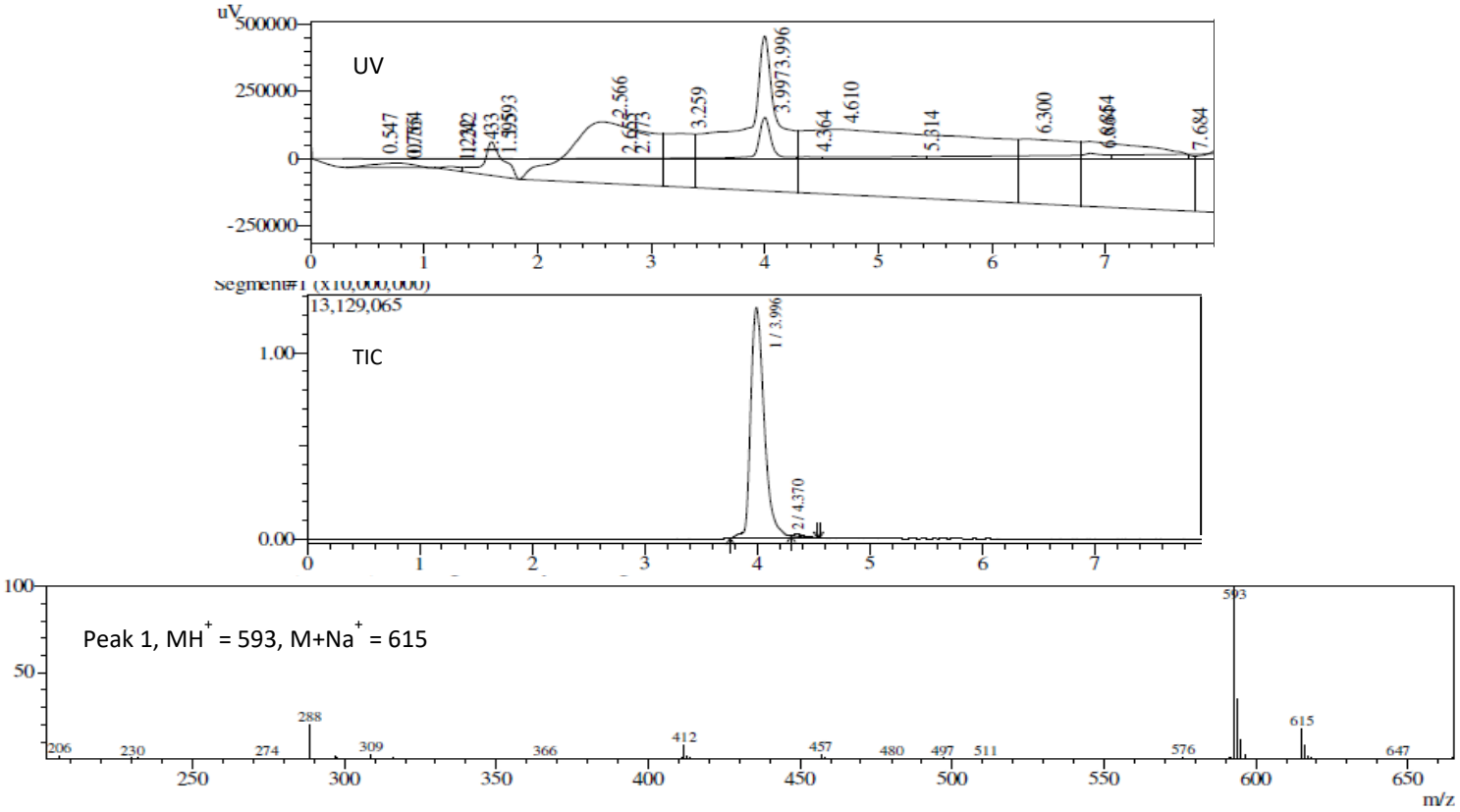
2317 - 24 PK 1 PURE, 300K, CDCL3

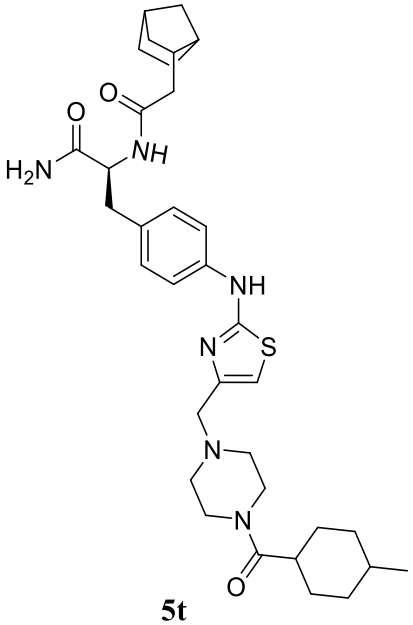


5s

2317 - 24 PK 1 PURE, 300K, CDCL3




uV
500000
250000
0
-250000
UV
0.547
3.433
2.566
3.259
3.9973.996
4.364
4.610
5.814
6.300
7.684
0
1
2
3
4
5
6
7
13,129,065
1.00
0.00
TIC
1 / 3.996
2 / 4.370
100
50
Peak 1, MH+ = 593, M+Na+ = 615
593
615
288
206
230
274
309
366
412
457
480
497
511
576
647
250
300
350
400
450
500
550
600
650
m/z



5t

$C_{34}H_{48}N_6O_3S$

Exact Mass: 620.35

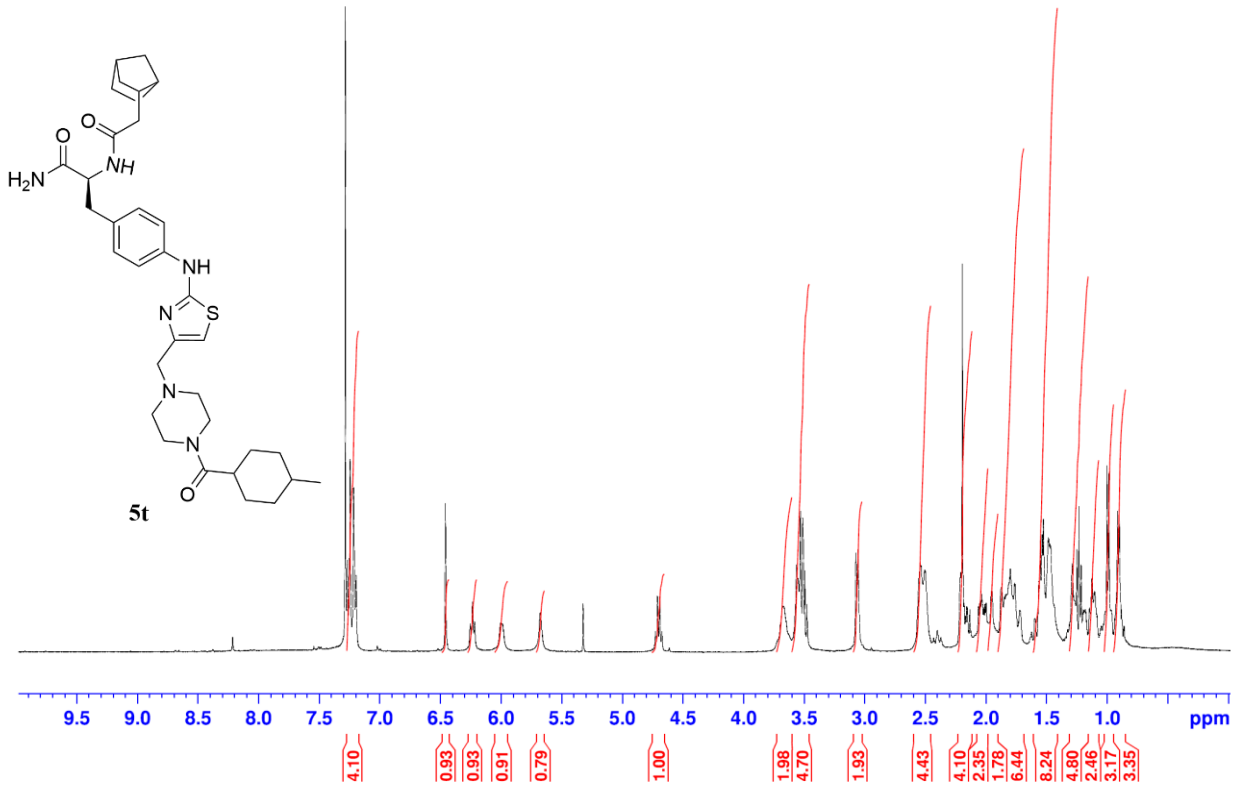
Mol. Wt.: 620.85

5t (¹H NMR, 400 MHz, $CDCl_3$, 300 K) δ 7.23 (q, J = 12.7 Hz, 4H), 6.46 (s, 1H), 6.24 (t, J = 9.5 Hz, 1H), 6.0 (d, J = 7.4 Hz, 1H), 6.68 (s_{broad}, 1H), 4.70 (q, J = 7.4 Hz, 1H), 3.67 ($s_{v.\ broad}$, 2H), 3.59-3.48 (m, 4H), 3.06 (d, J = 7.4 Hz, 2H), 2.54 (s_{broad}, 2H), 2.50 (s_{broad}, 2H), 2.23 (s_{broad}, 2H), 2.19 (s, 2H), 2.17-2.13 (m, 1H), 2.07-1.99 (m, 1H), 1.95 (s_{borad}, 2H), 1.87 (s_{broad}, 2H), 1.85 – 1.70 (m, 6H), 1.57-1.42 (m, 8H), 1.32 – 1.06 (m, 7H), 0.99 (d, J = 7.5 Hz, 3H), 094-0.88 (m, 3H)

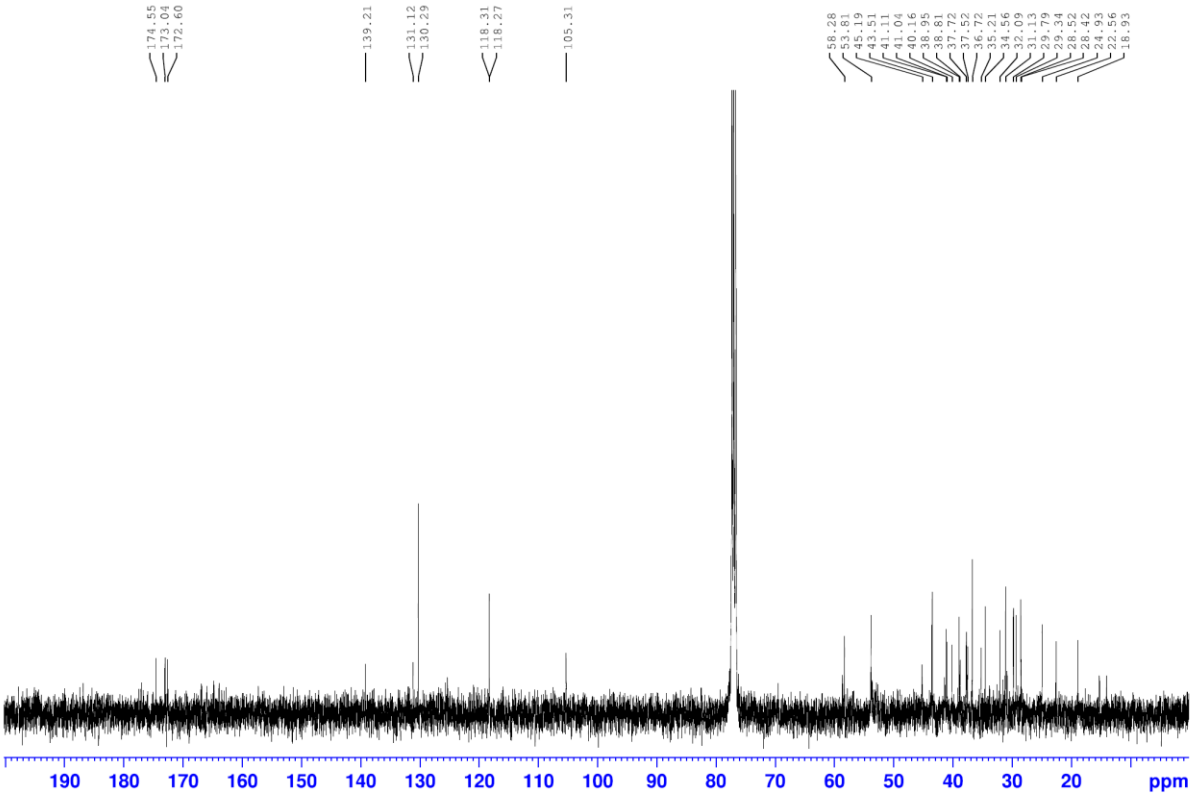
5t (¹³C NMR, 100 MHz, $CDCl_3$, 300 K) δ 174.5, 173.0, 172.6, 139.2, 131.1, 130.3, 118.3, 118.2, 105.3, 58.3, 53.8, 45.2, 43.5, 41.1, 41.0, 40.2, 39.0, 38.8, 37.7, 37.5, 36.7, 35.2, 31.1, 29.8, 29.3, 28.5, 28.4, 24.9, 22.6, 18.9

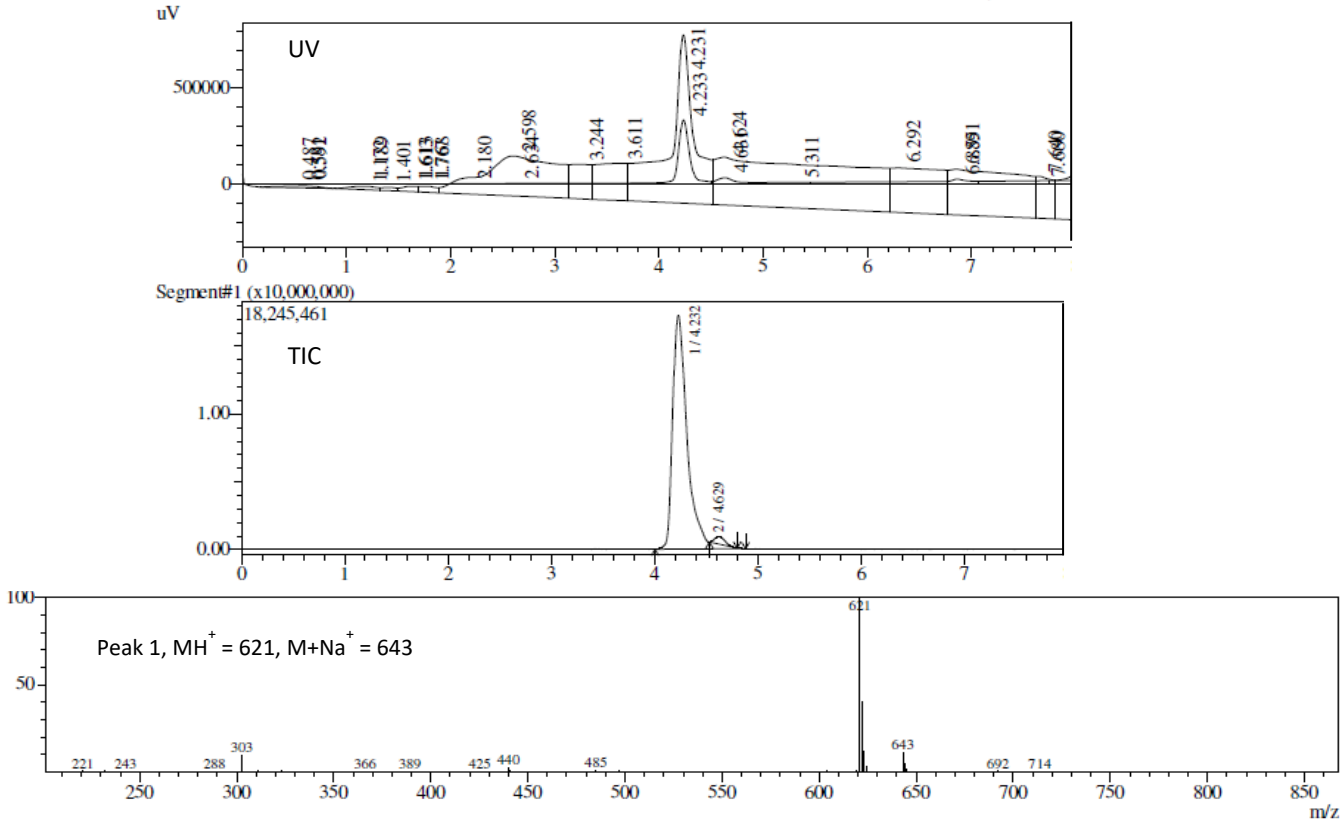
LCMS: $C_{34}H_{48}N_6O_3S$ (M calculated) 620.85, $C_{34}H_{49}N_6O_3S$ (MH^+ found) 621

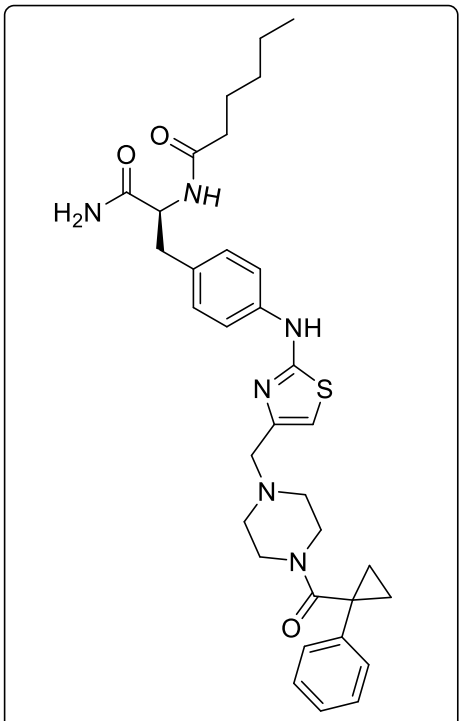
2317 - 25 PURE, 300K, CDCL3



2317 - 25 PURE, 300K, CDCL3




uV
UV
500000
0
4.233
4.231
3.244
3.611
2.180
6.292
5.311
0
1
2
3
4
5
6
7
Segment#1 (x10,000,000)
18,245,461
TIC
1.00
0.00
1 / 4.232
2 / 4.629
100
50
621
Peak 1, MH+ = 621, M+Na+ = 643
643
303
221
243
288
366
389
425
440
485
692
714
250
300
350
400
450
500
550
600
650
700
750
800
850
m/z



5u

$C_{33}H_{42}N_6O_3S$

Exact Mass: 602.30

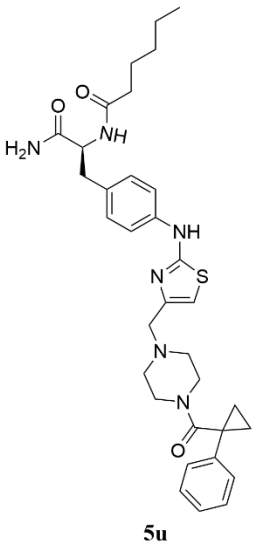
Mol. Wt.: 602.79

5u (^{1}H NMR, 400 MHz, $CDCl_3$, 300 K) δ 7.29 (d, J = 6.40 Hz, 2H), 7.22 (d, J = 3.4 Hz, 4H), 7.17 (d, J = 7.4 Hz, 2H), 6.41 (s, 1H), 6.22 (d, J = 8.9 Hz, 1H), 5.94 (s_{broad}, 1H), 5.62 (s_{broad}, 1H), 4.69 (q, J = 8.9 Hz, 1H), 3.71 (s_{broad}, 2H), 3.51 (pent, J = 7.8 Hz, 2H), 3.44 (d, J = 4.3 Hz, 2H), 3.06 (t, J = 5.8 Hz, 2H), 2.50 (s_{broad}, 2H), 2.20 (t, J = 5.3 Hz, 5H), 1.61 (pent, J = 7.3 Hz, 2H), 1.44 – 1.41 (m, 2H), 1.35 – 1.22 (m, 6H), 1.22-1.17 (m, 2H), 0.89 (t, J = 6.6 Hz, 4H)

5u (^{13}C NMR, 100 MHz, $CDCl_3$, 300 K) δ 173.2, 173.0, 170.9, 164.7, 140.7, 139.2, 131.1, 130.3, 128.7, 126.3, 125.3, 118.3, 105.3, 58.2, 53.9, 52.6, 37.6, 36.5, 31.3, 29.4, 25.2, 22.3, 15.2, 13.9

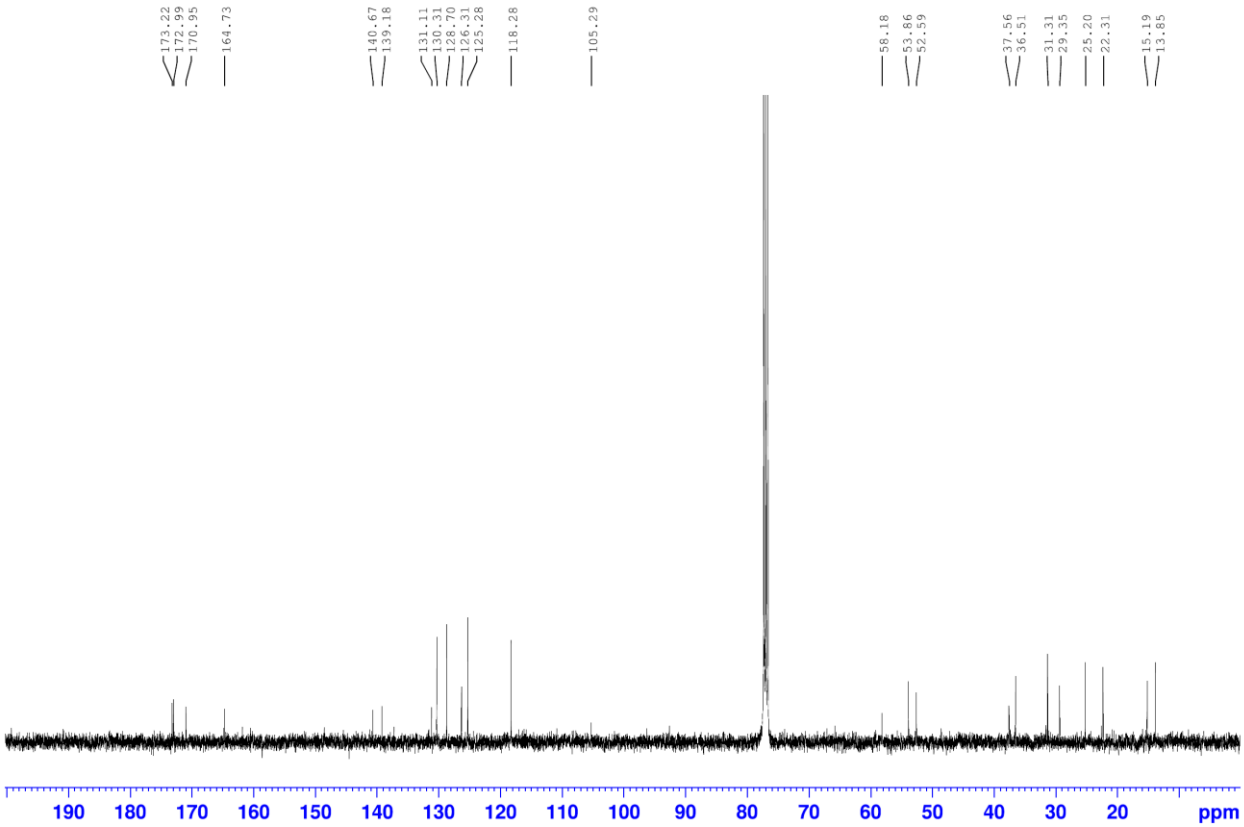
LCMS: $C_{33}H_{42}N_6O_3S$ (M calculated) 602.79, $C_{33}H_{43}N_6O_3S$ (MH^+ found) 603

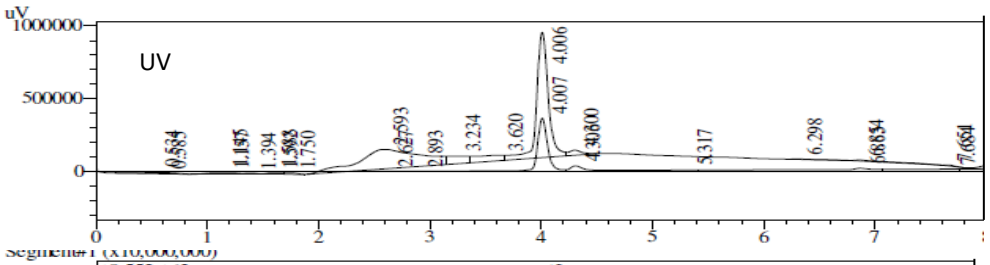
2317 - 26 PURE, 300K, CDCL3

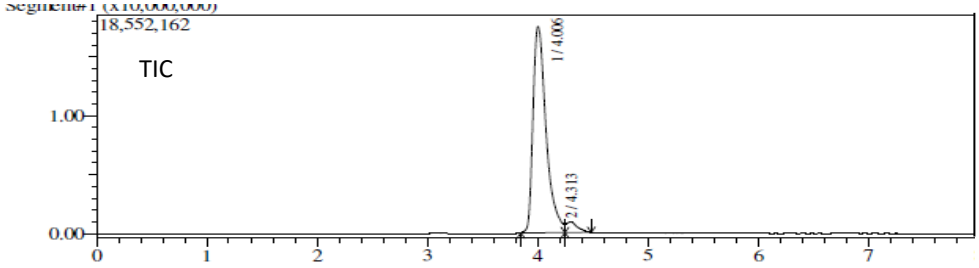


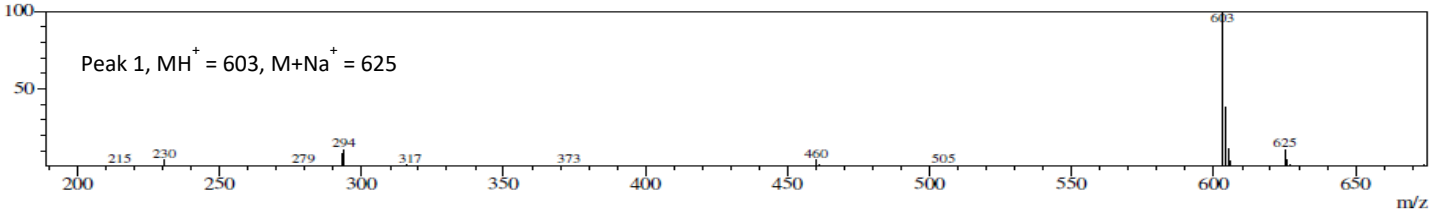
5u

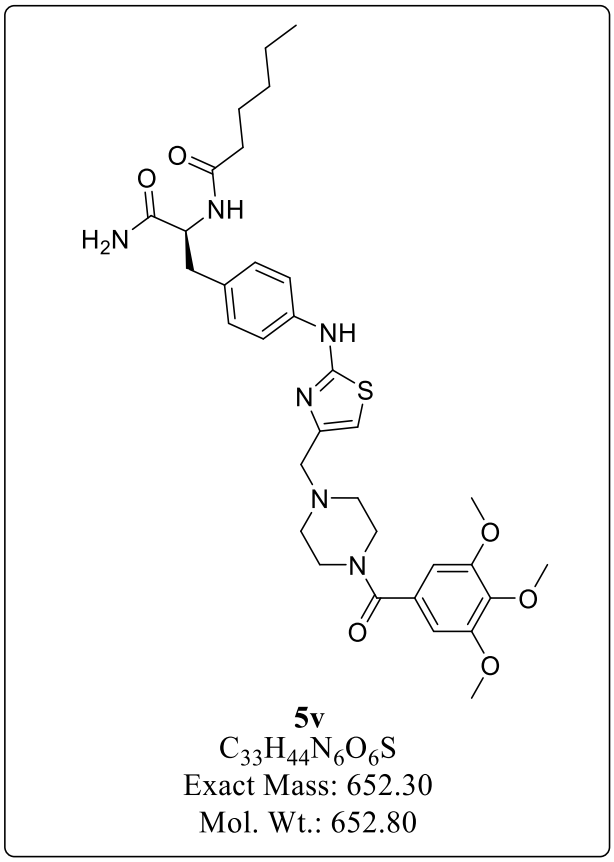
2317 - 26 PURE, 300K, CDCL3




uV
1000000
500000
0
UV
4.006
4.007
3.620
3.234
2.893
1.750
5.317
6.298
0
1
2
3
4
5
6
7


18,552,162
TIC
1.00
0.00
1/4.006
2/4.313
0
1
2
3
4
5
6
7


100
50
Peak 1, MH+ = 603, M+Na+ = 625
603
625
215
230
279
294
317
373
460
505
200
250
300
350
400
450
500
550
600
650
m/z



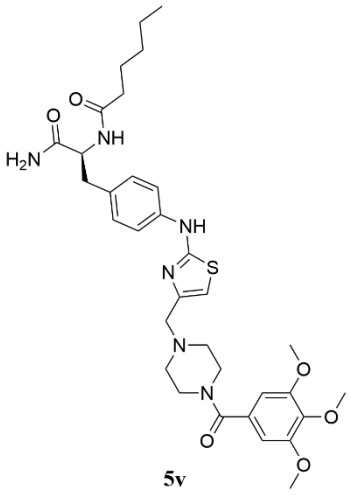
5v
$C_{33}H_{44}N_6O_6S$
Exact Mass: 652.30
Mol. Wt.: 652.80

5v (^{1}H NMR, 400 MHz, $CDCl_3$, 300 K) δ 7.23 (q, J = 7.6 Hz, 4H), 6.64 (s, 2H), 6.46 (s, 1H), 6.22 (d, J = 7.6 Hz, 1H), 5.93 (s_{broad}, 1H), 5.63 (s_{broad}, 1H), 4.69 (q, J = 8.1 Hz, 1H), 3.88 (s, 6H), 3.87 (s, 3H), 3.55 (d, J = 4.5 Hz, 2H), 3.53 – 3.48 (m, 1H), 3.09-3.04 (m, 2H), 2.56 ($s_{v.broad}$, 4H), 2.20 (t, J = 6.7 Hz, 3H), 1.61 (pent, J = 8.9 Hz, 1H), 1.36 – 1.21 (m, 6H), 0.89 (t, J = 6.7 Hz, 4H)

5v (^{13}C NMR, 100 MHz, $CDCl_3$, 300 K) δ 173.2, 173.0, 170.1, 153.3, 139.4, 139.1, 131.2, 131.1, 130.3, 118.3, 104.6, 60.9, 58.2, 56.3, 53.9, 37.5, 36.5, 31.3, 25.2, 22.3, 13.9

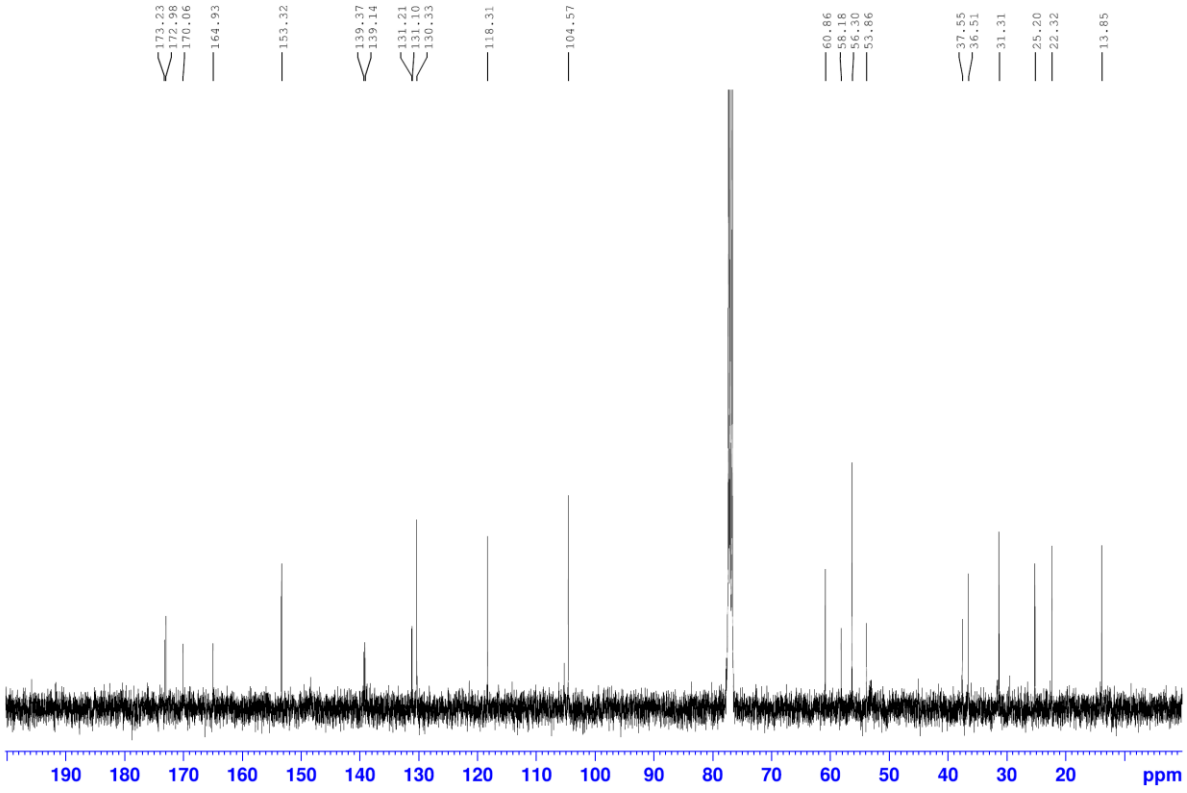
LCMS: $C_{33}H_{44}N_6O_6S$ (M calculated) 652.80, $C_{33}H_{45}N_6O_6S$ (MH^+ found) 653

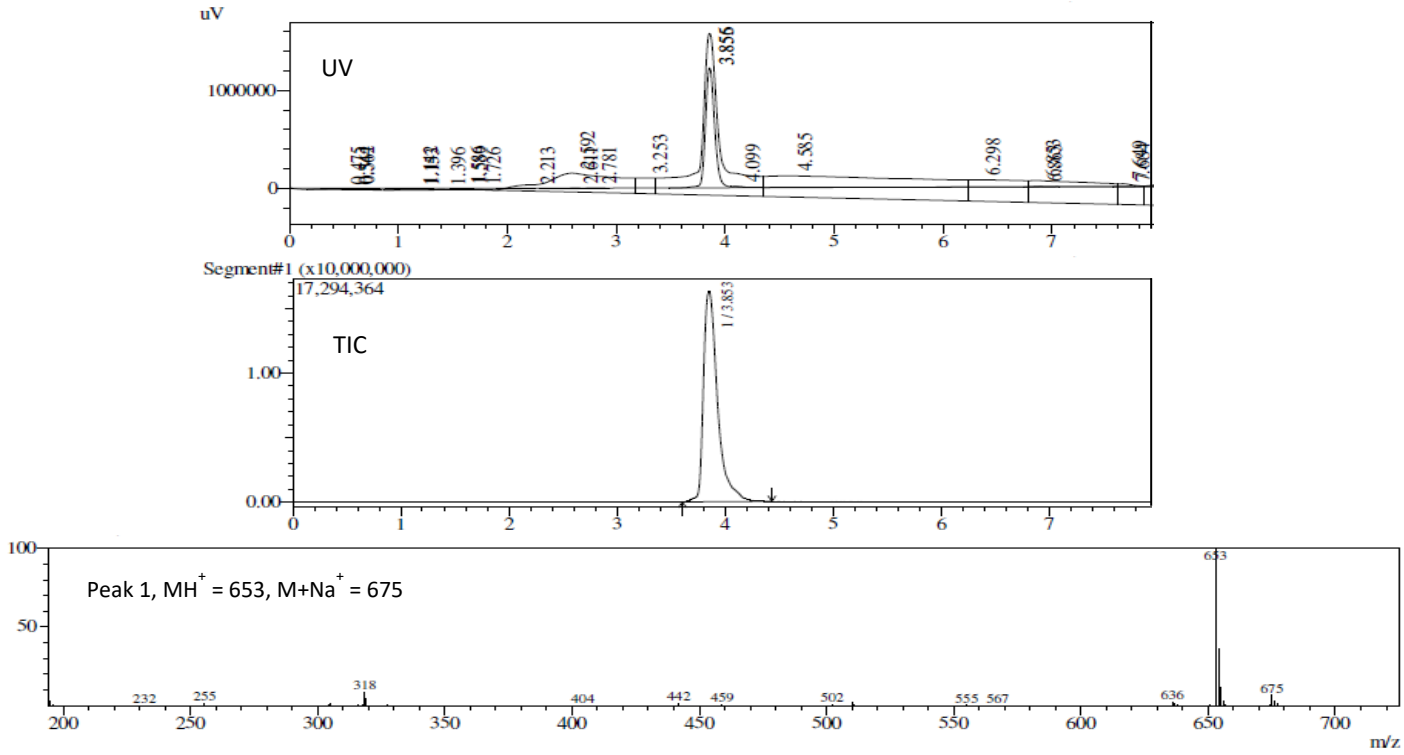
2317 - 28 PURE, 300K, CDCL3

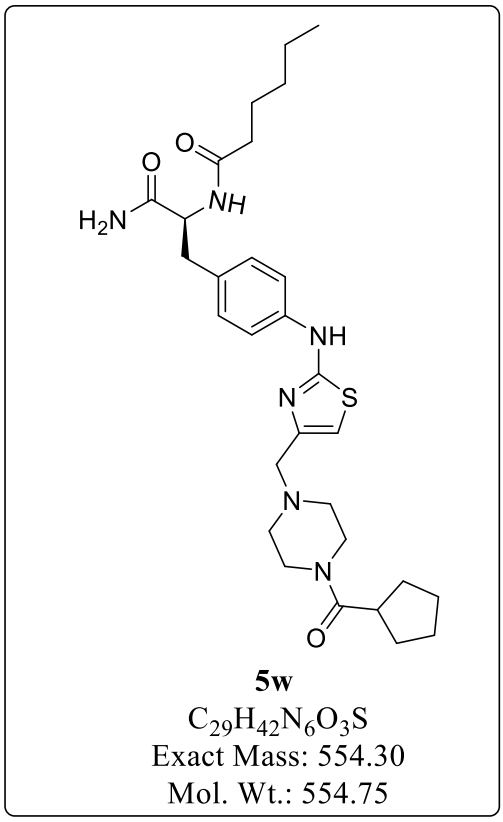


5v

2317 - 28 PURE, 300K, CDCL3




uV
UV
1000000
0
3.856
4.099
4.585
6.298
3.253
2.781
2.213
1.396
0 1 2 3 4 5 6 7
Segment#1 (x10,000,000)
17,294,364
TIC
1.00
0.00
1 / 3.853
0 1 2 3 4 5 6 7
100
50
Peak 1, MH+ = 653, M+Na+ = 675
653
675
636
555 567
502
442 459
404
318
232 255
200 250 300 350 400 450 500 550 600 650 700
m/z

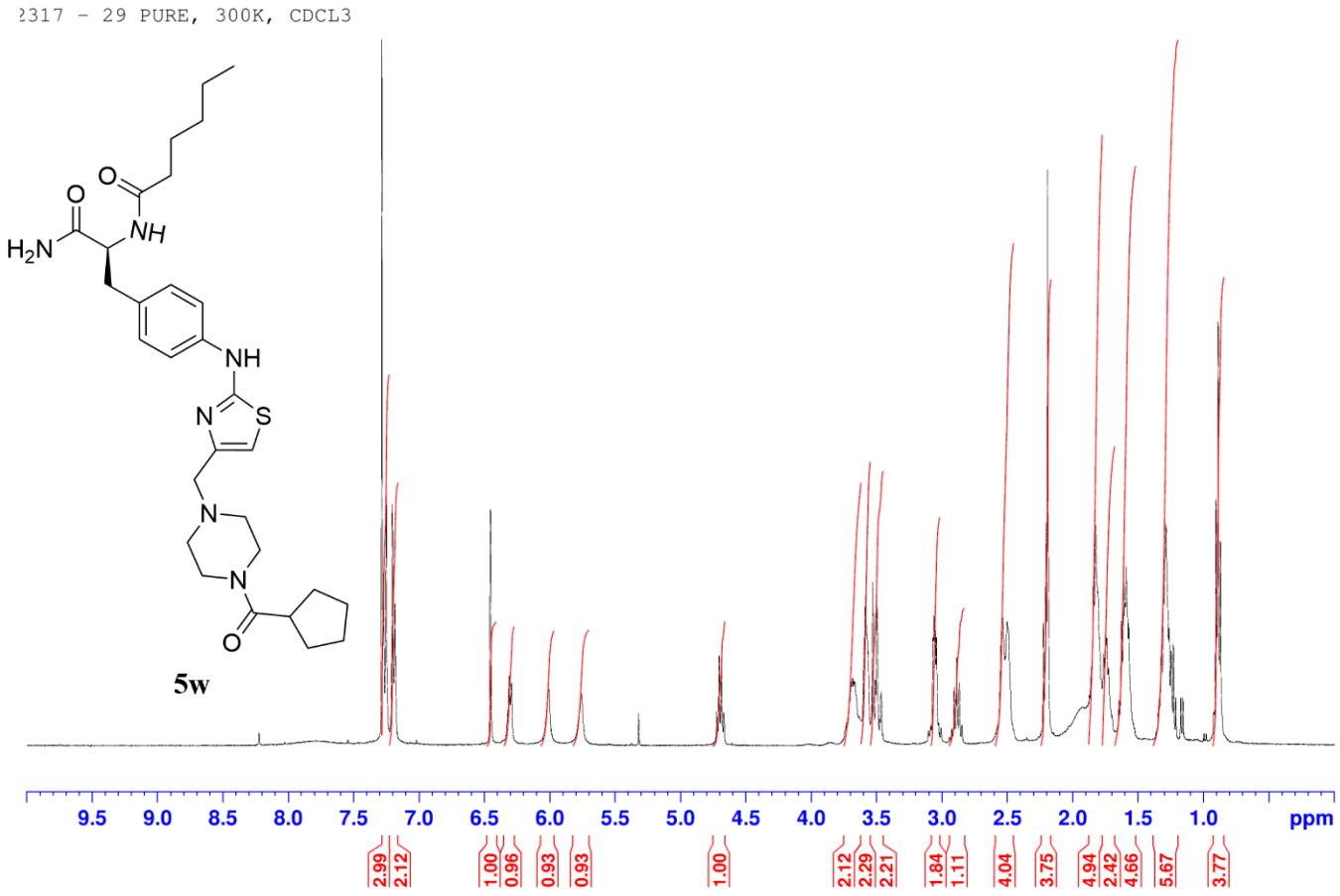


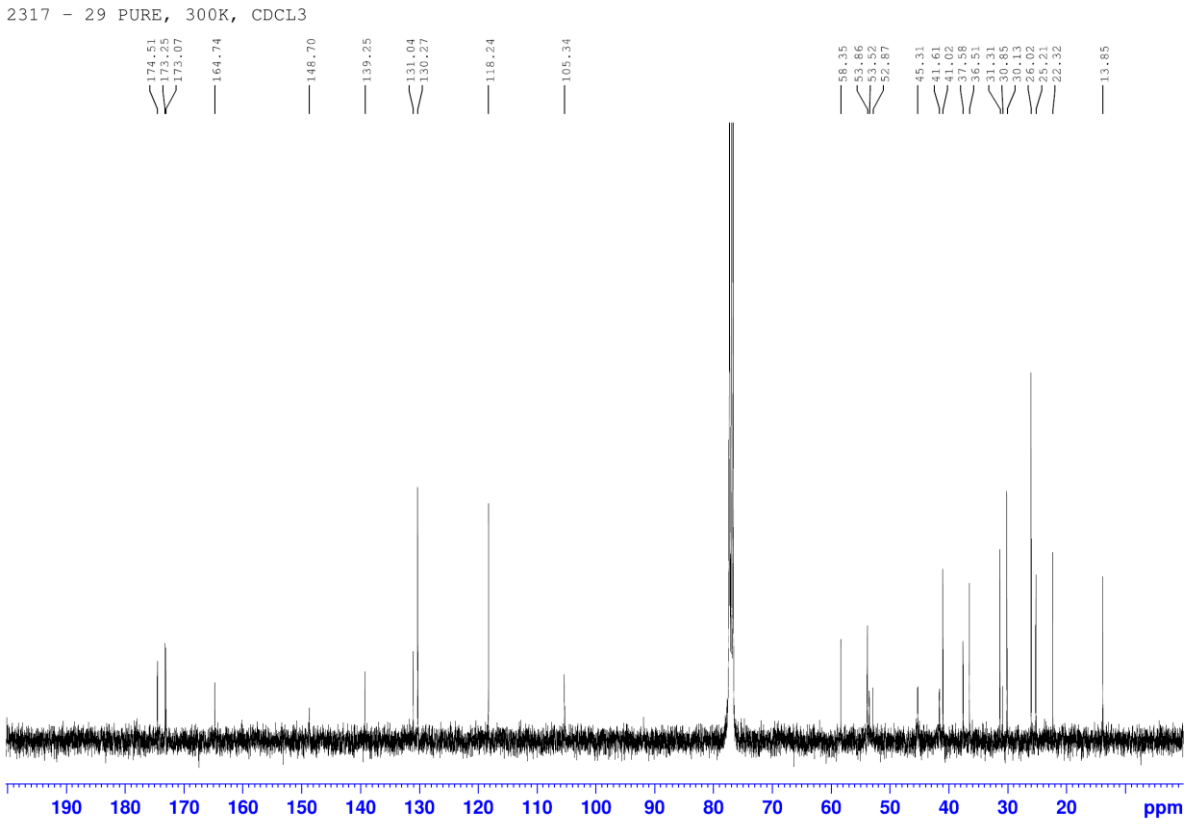
5w
$C_{29}H_{42}N_6O_3S$
Exact Mass: 554.30
Mol. Wt.: 554.75

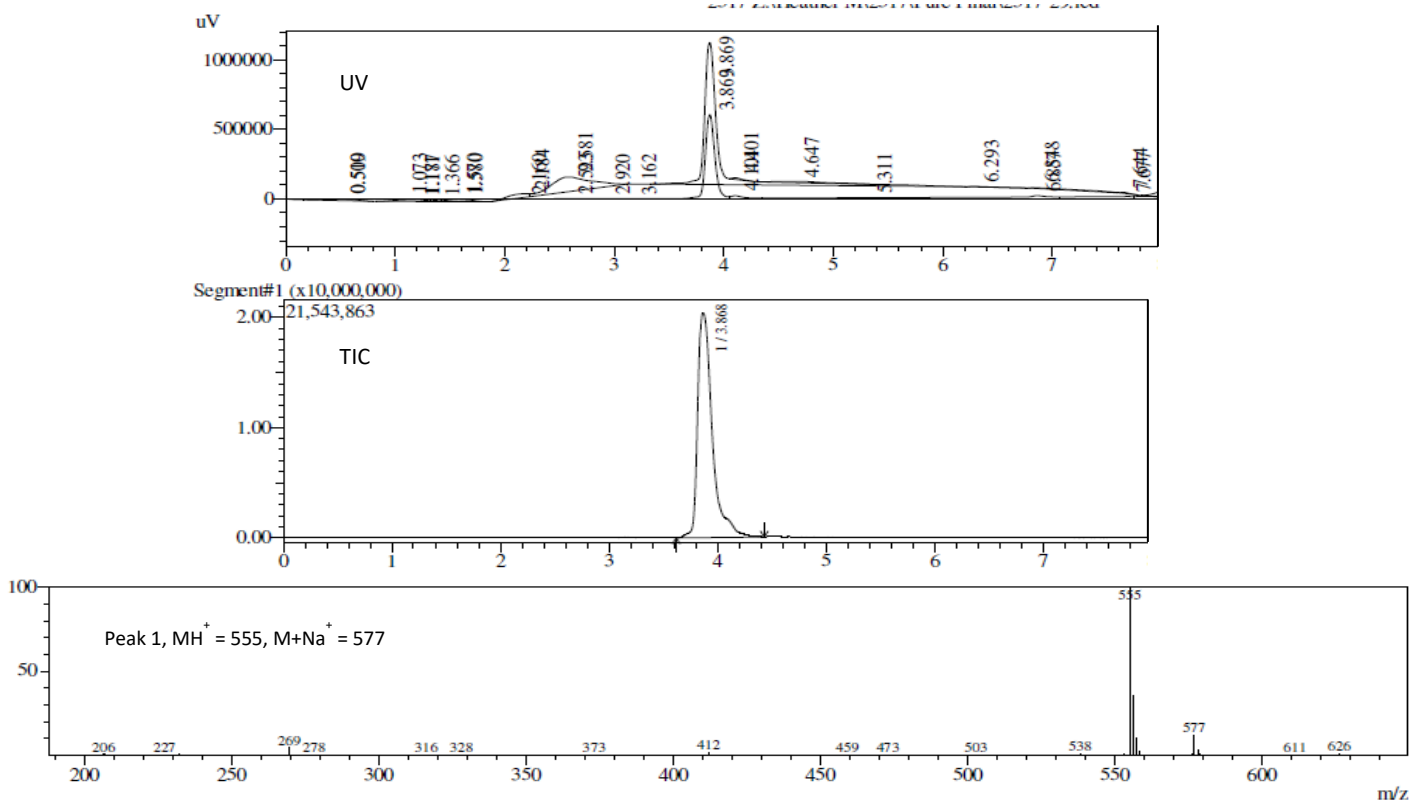
5w (¹H NMR, 400 MHz, $CDCl_3$, 300 K) δ 7.27 (d, J = 7.0 Hz, 2H), 7.20 (d, J = 7.7 Hz, 2H), 6.45 (s, 2H), 6.30 (d, J = 9.8 Hz, 1H), 6.02 (s_{broad}, 1H), 5.76 (s_{broad}, 1H), 4.70 (q, J = 7.7 Hz, 1H), 3.76-3.65 (m, 2H), 3.61-3.55 (m, 2H), 3.52 (d, J = 11.5 Hz, 2H), 3.09-3.03 (m, 2H), 2.89 (pent, J = 8.5 Hz, 1H), 2.54 (s_{broad}, 2H), 2.50 ($s_{broad, 2H)}$, 2.21 (t, J = 7.7 Hz, 2H), 2.19 (s, 2H), 1.88-1.72 (7H), 1.66-1.55 (m, 5H), 1.36-1.21 (m, 5H), 0.89 (t, J = 6.6 Hz, 3H)

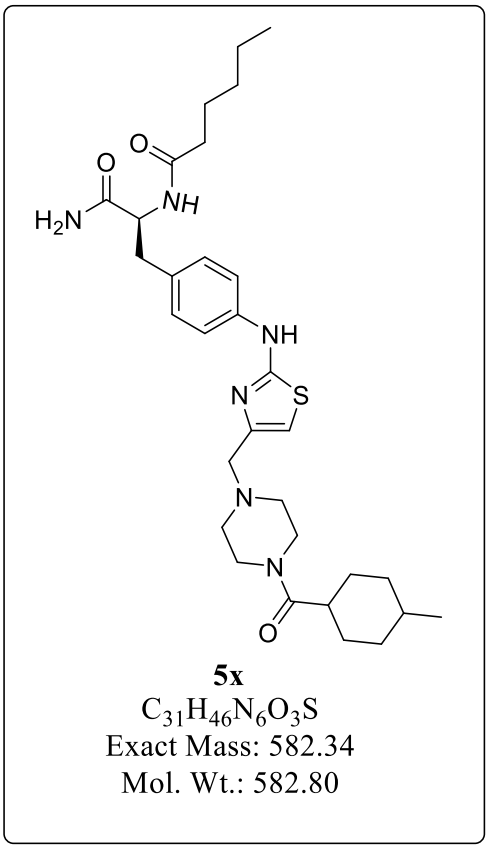
5w (¹³C NMR, 100 MHz, $CDCl_3$, 300 K) δ 174.5, 173.2, 173.1, 164.7, 148.7, 139.3, 131.0, 130.3, 118.2, 105.3, 58.3, 53.9, 53.5, 52.9, 45.3, 41.6, 41.0, 37.6, 36.5, 31.3, 30.8, 30.1, 26.0, 25.2, 22.3, 13.9

LCMS: $C_{29}H_{42}N_6O_3S$ (M calculated) 554.75, $C_{29}H_{43}N_6O_3S$ (MH^+ found) 555


2317 - 29 PURE, 300K, CDCL3
O
NH
H2N
O
NH
N
S
N
N
O
5w
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
2.99 2.12 1.00 0.96 0.93 0.93 1.00 2.12 2.29 2.21 1.84 1.11 4.04 3.75 4.94 2.42 4.66 5.67 3.77


2317 - 29 PURE, 300K, CDCL3
174.51
173.25
173.07
164.74
148.70
139.25
131.04
130.27
118.24
105.34
58.35
53.86
53.52
52.87
45.31
41.61
41.02
37.58
36.51
31.31
30.85
30.13
26.02
25.21
22.32
13.85
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm


uV
1000000
500000
0
UV
3.869
4.647
6.293
0 1 2 3 4 5 6 7
Segment#1 (x10,000,000)
2.00
1.00
0.00
21,543,863
TIC
3.868
0 1 2 3 4 5 6 7
100
50
Peak 1, MH+ = 555, M+Na+ = 577
555
577
206 227 269 278 316 328 373 412 459 473 503 538 611 626
200 250 300 350 400 450 500 550 600
m/z



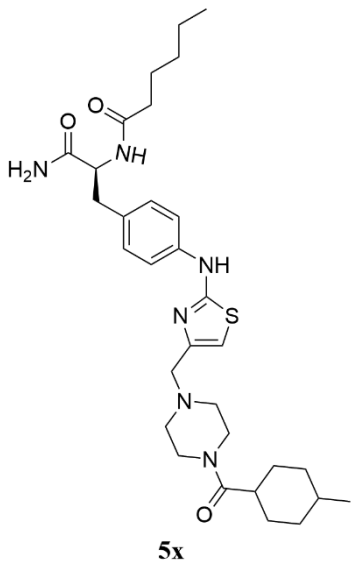
5x
$C_{31}H_{46}N_6O_3S$
Exact Mass: 582.34
Mol. Wt.: 582.80

5x (^{1}H NMR, 400 MHz, $CDCl_3$, 300 K) δ 7.26 (d, J = 8.0 Hz, 2H), 7.20 (d, J = 8.7 Hz, 2H), 6.45 (s, 1H), 6.27 (d, J = 8.0 Hz, 1H), 5.97 (s_{broad}, 1H), 5.71 (s_{broad}, 1H), 4.69 (q, J = 9.8 Hz, 1H), 3.67 (s_{vbroad}, 2H), 3.59 – 3.46 (m, 4H), 3.06 (t, J = 5.4 Hz, 2H), 2.55 (s_{broad}, 2H), 2.50 (s_{broad}, 2H), 2.21 (d, J = 7.3 Hz, 1H), 2.19 (s, 3H), 1.90 ($S_{v.broad}$, 2H), 1.85-1.72 (m, 5H), 1.65-1.47 (m, 7H), 1.34-1.23 (m, 5H), 0.99 (d, J = 7.9 Hz, 3H), 0.89 (t, J = 7.1 Hz, 3H)

5x (^{13}C NMR, 100 MHz, $CDCl_3$, 300 K) δ 174.5, 173.2, 173.0, 164.7, 148.8, 139.2, 131.1, 130.3, 118.2, 105.3, 58.4, 53.9, 40.2, 38.8, 37.6, 36.5, 34.6, 32.1, 30.9, 29.3, 28.4, 25.2, 24.9, 22.6, 22.3, 18.9, 13.9

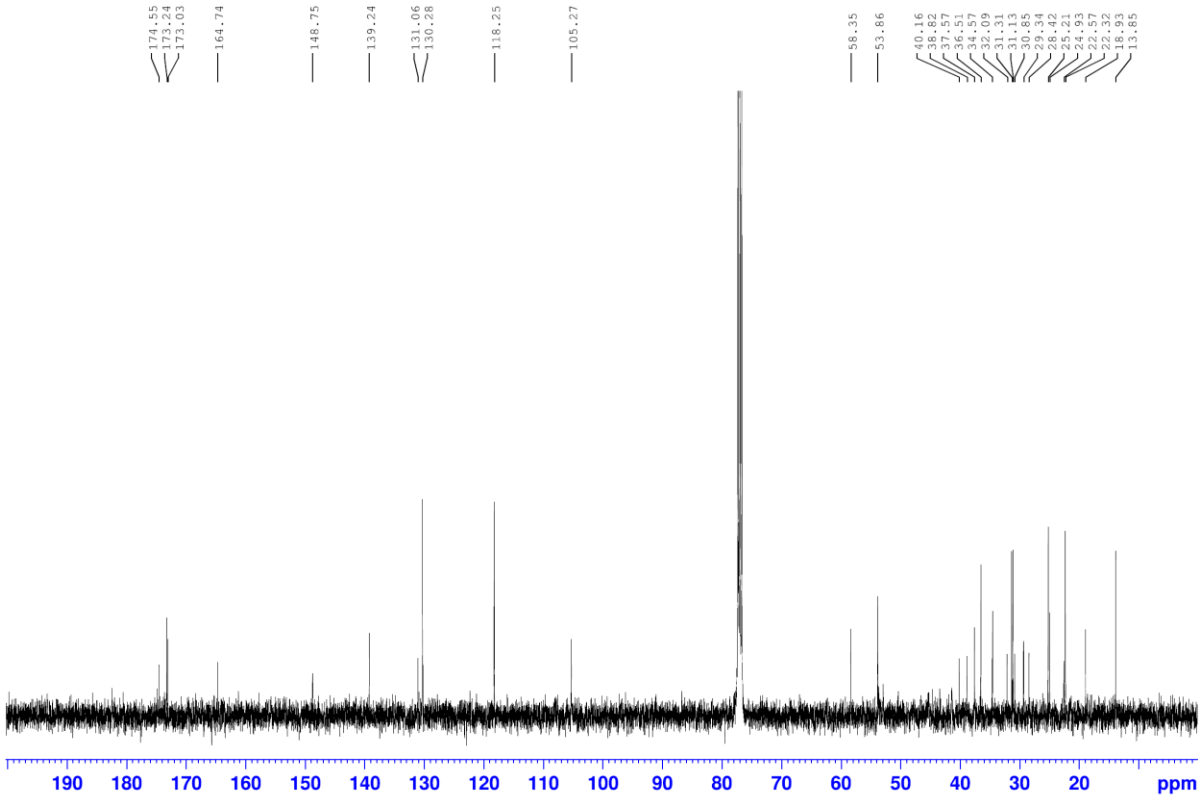
LCMS: $C_{31}H_{46}N_6O_3S$ (M calculated) 582.80, $C_{31}H_{47}N_6O_3S$ (MH^+ found) 583

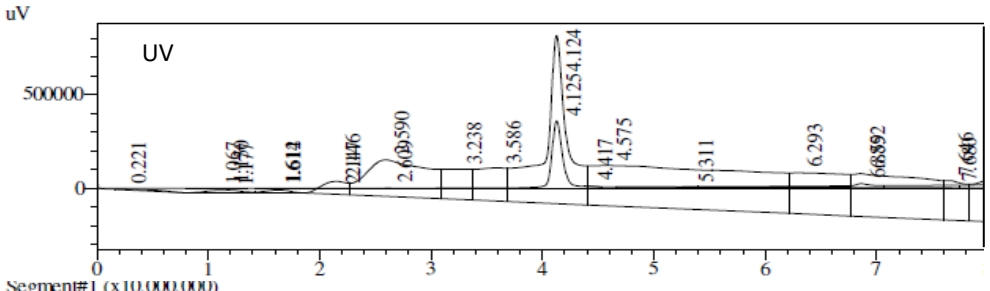
2317 - 30 PURE, 300K, CDCL3

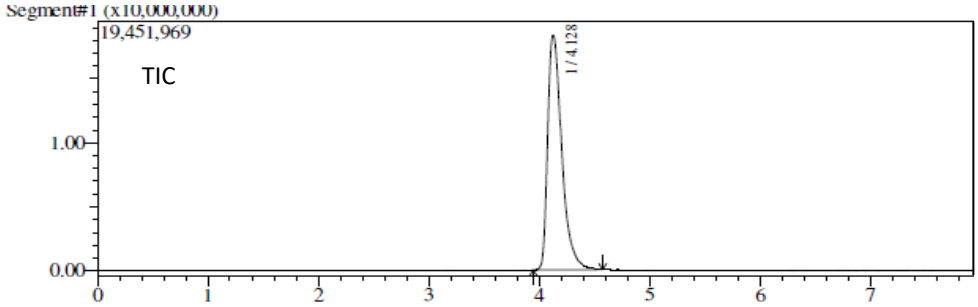


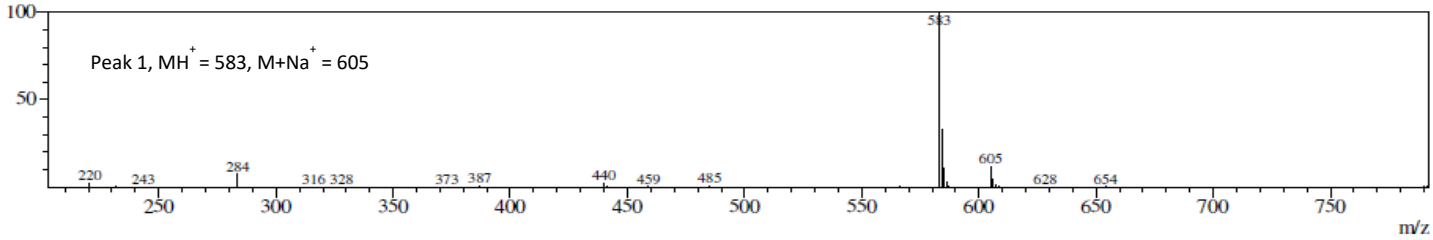
5x

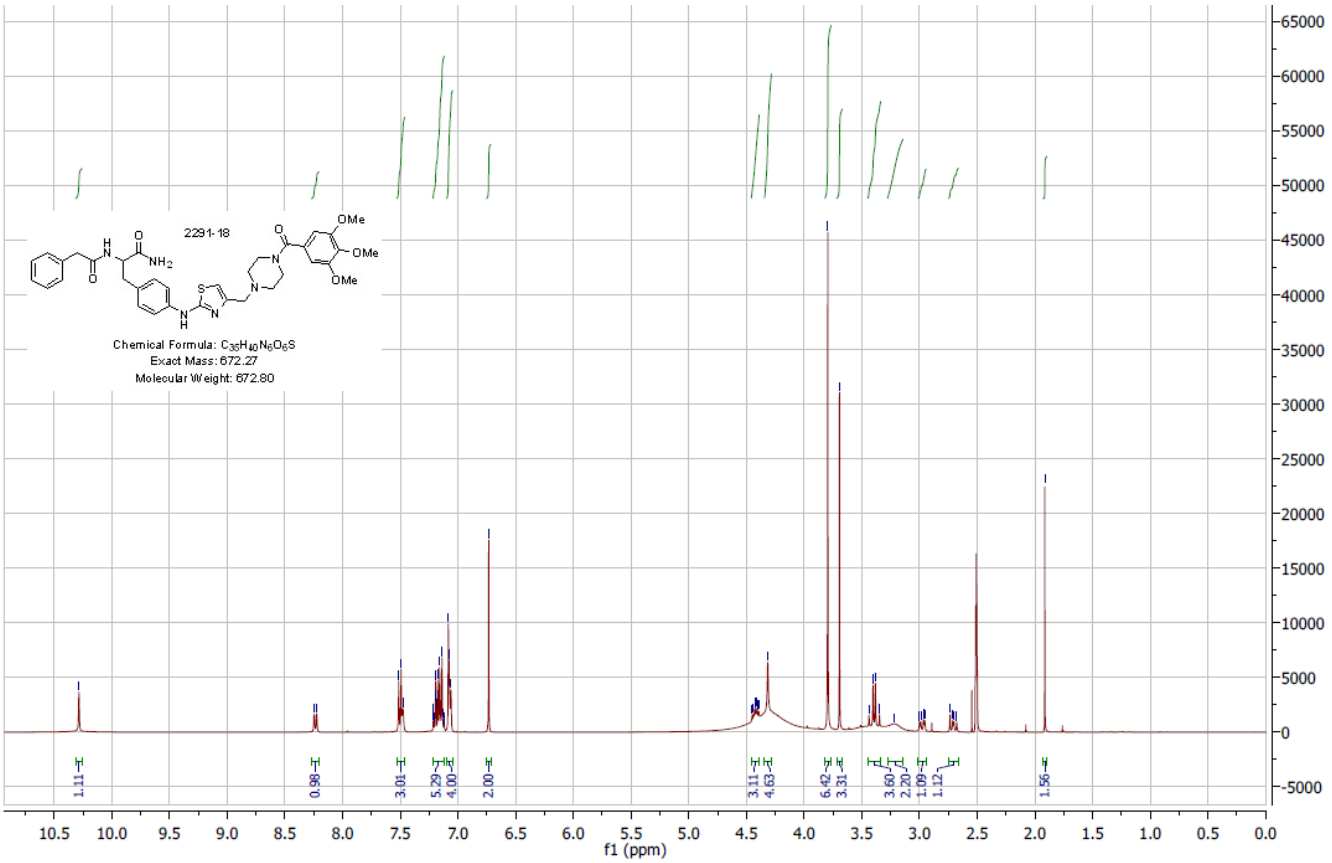
2317 - 30 PURE, 300K, CDCL3

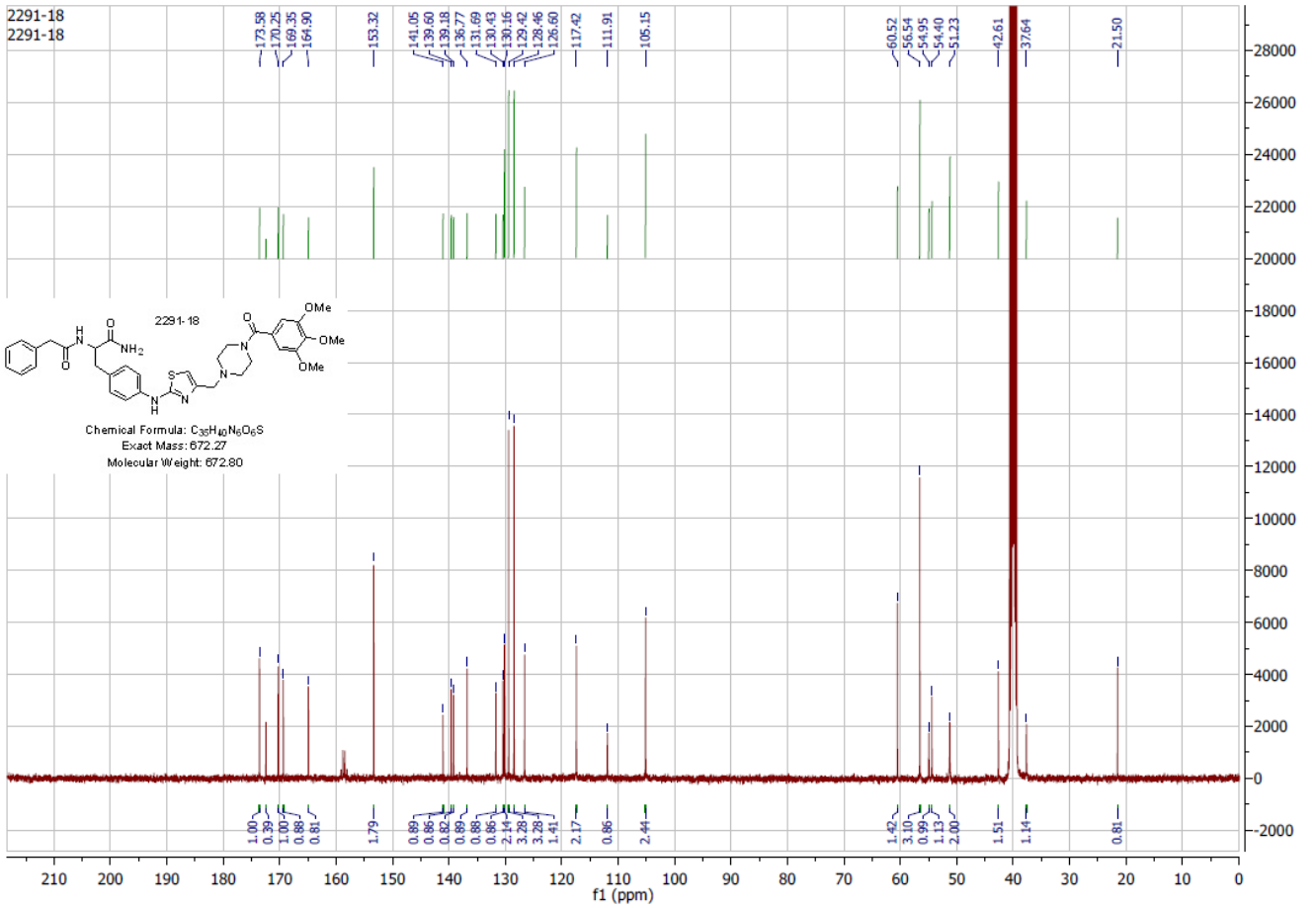


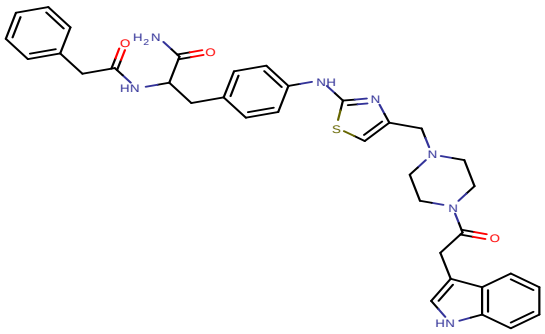
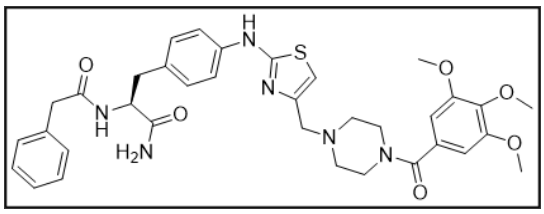
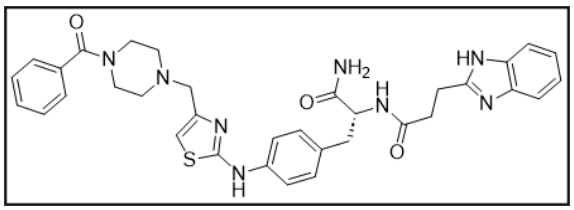
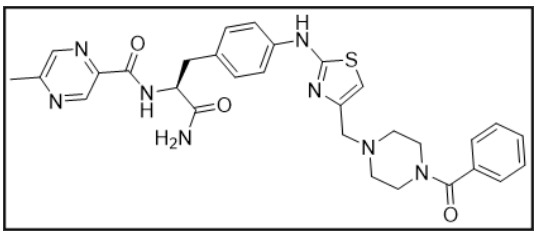

uV
UV
500000
0
0.221
1.612
2.609
3.238
3.586
4.125
4.124
4.417
4.575
5.311
6.293
0
1
2
3
4
5
6
7

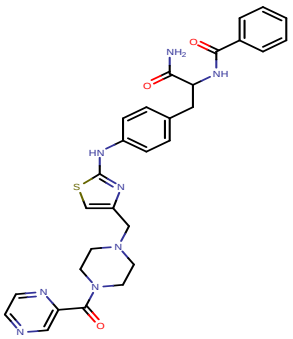
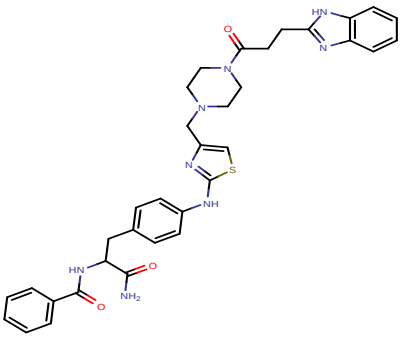
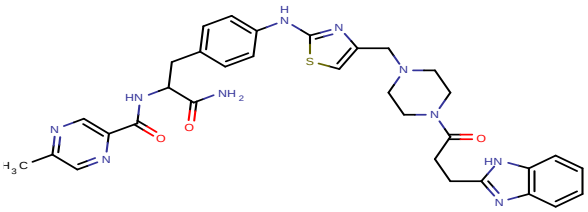
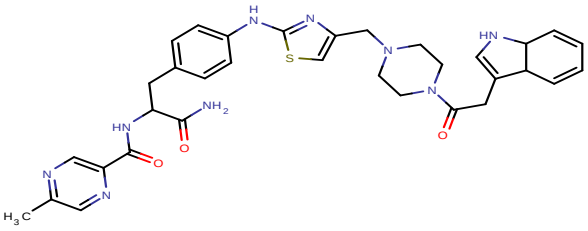

Segment#1 (x10,000,000)
19,451,969
TIC
1 / 4.128
1.00
0.00
0
1
2
3
4
5
6
7

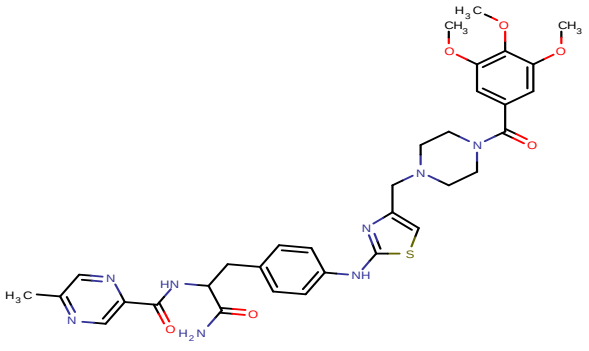
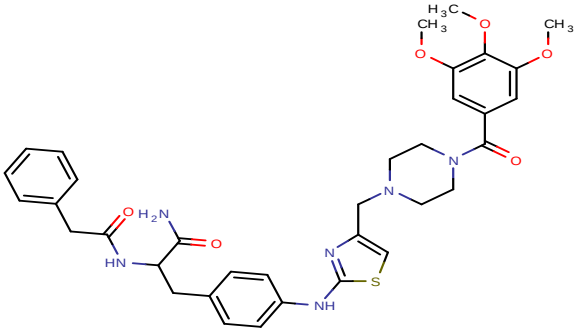
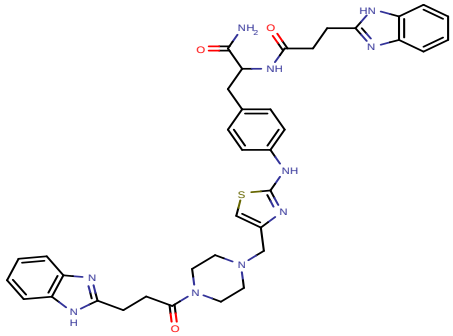
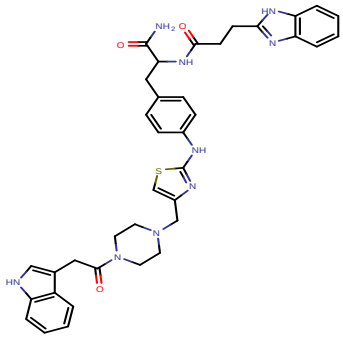

100
50
Peak 1, MH+ = 583, M+Na+ = 605
583
605
220
243
284
316 328
373 387
440
459
485
628
654
250
300
350
400
450
500
550
600
650
700
750
m/z

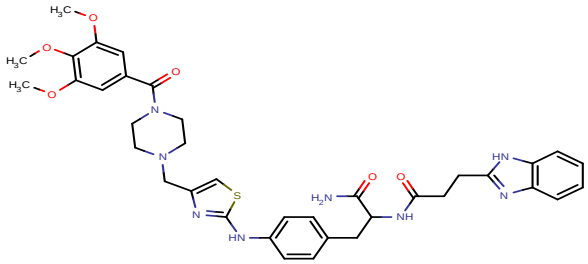
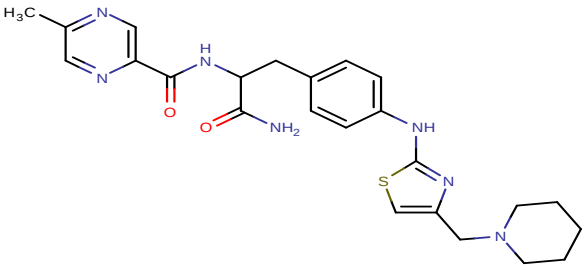
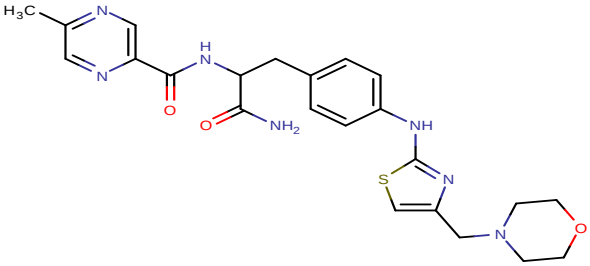
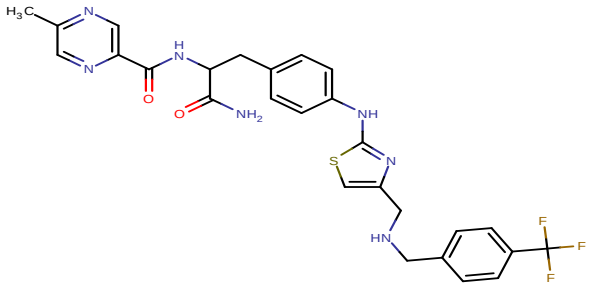

2291-18
Chemical Formula: C35H40N6O6S
Exact Mass: 672.27
Molecular Weight: 672.80
f1 (ppm)

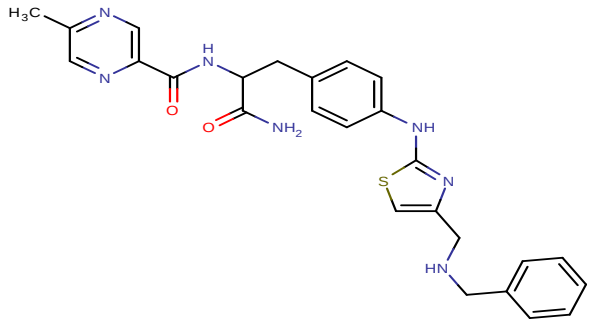
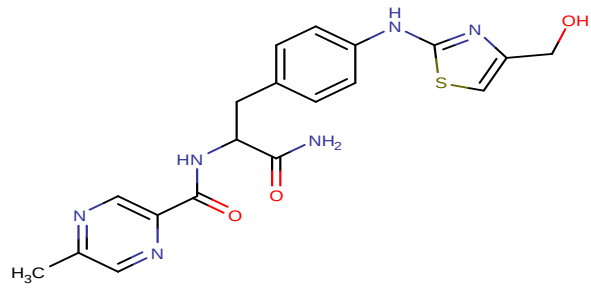
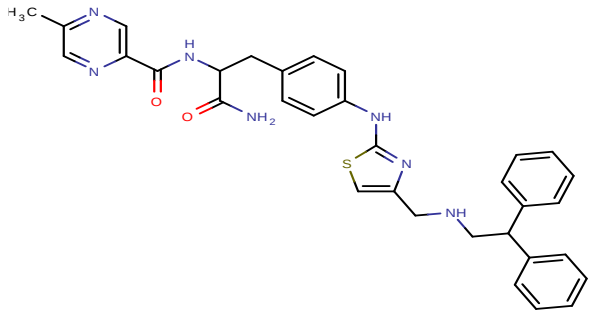
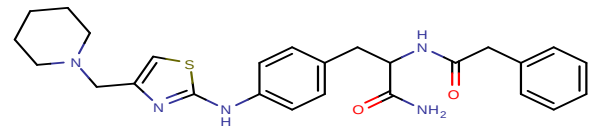

2291-18
2291-18
Chemical Formula: C35H40N6O6S
Exact Mass: 672.27
Molecular Weight: 672.80
f1 (ppm)

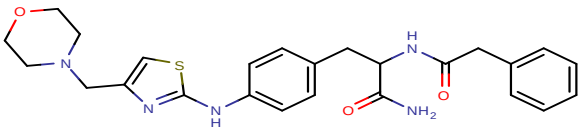
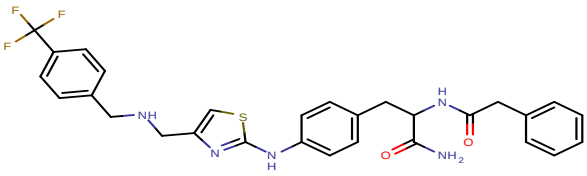
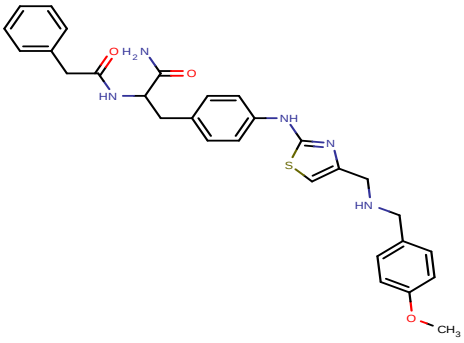
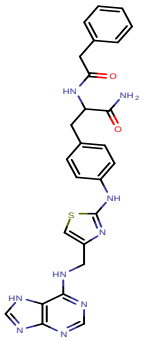
Compound ID Library 2291	Structure	Dd2 EC50 (μM) n=3
2291-61		0.102 ± 0.01
2291-18		0.220 ± 0.02
2291-135		0.190 ± 0.01
2291-134		0.200 ± 0.01

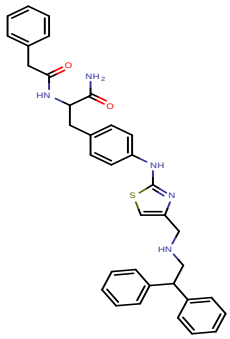
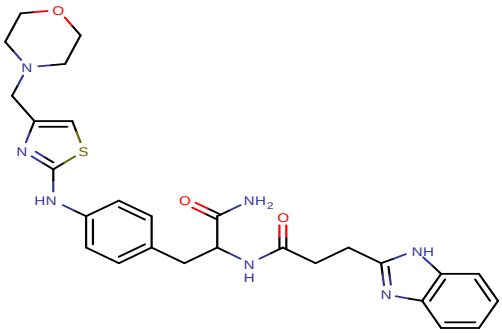
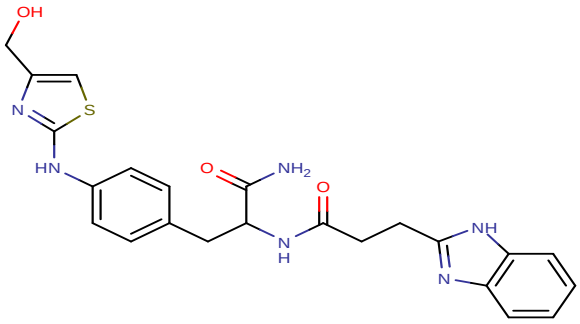
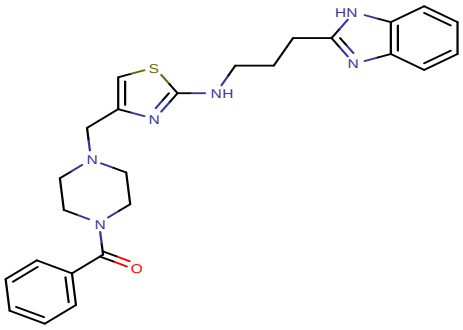
SB1-1		**0.836 ± 0.11**
SB1-2		**0.520 ± 0.08**
SB1-3		**>2.5**
SB1-4		**0.104 ± 0.03**

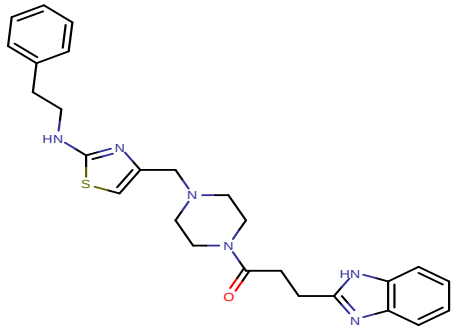
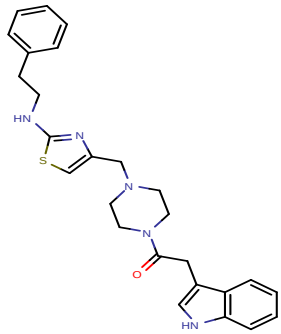
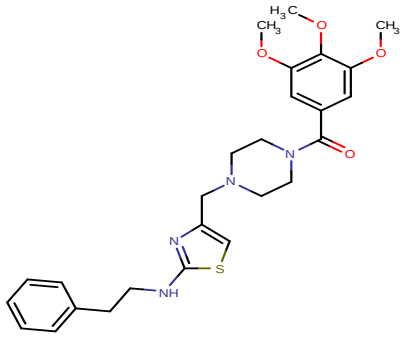
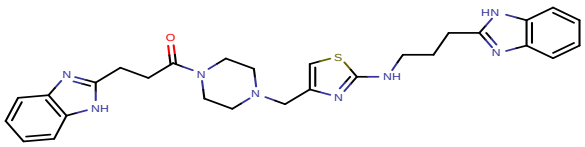
SB1-5		**1.02 ± 0.3**
SB1-8		**0.698 ± 0.03**
SB1-9		**0.132 ± 0.03**
SB1-10		**0.317 ± 0.08**

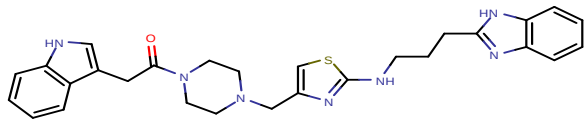
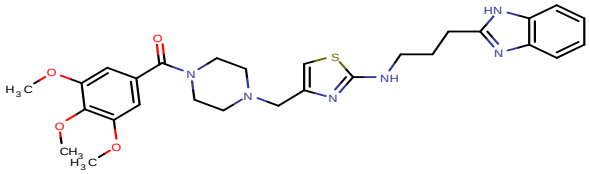
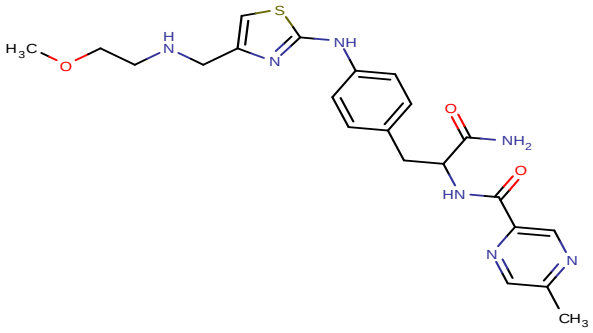
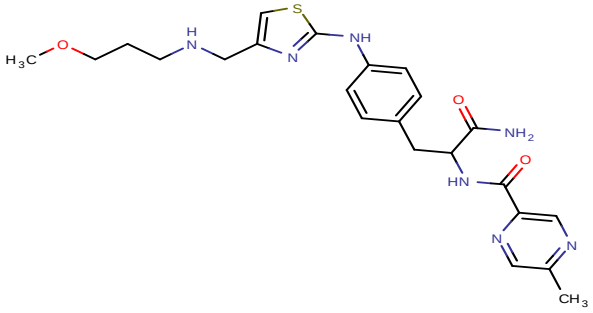
SB1-11		**0.381 ± 0.04**
SB1-12		**0.562 ± 0.06**
SB1-13		**0.250 ± 0.08**
SB1-14		**0.682 ± 0.15**

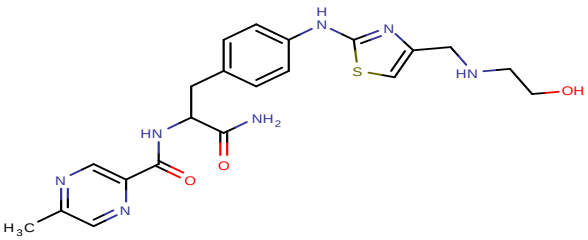
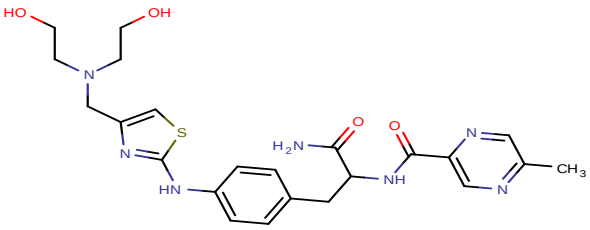
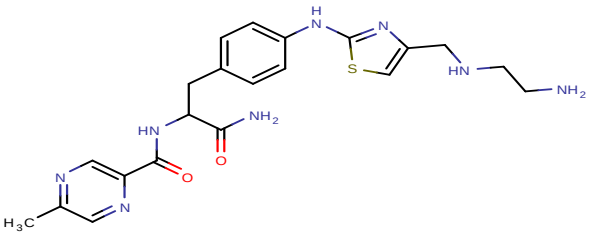
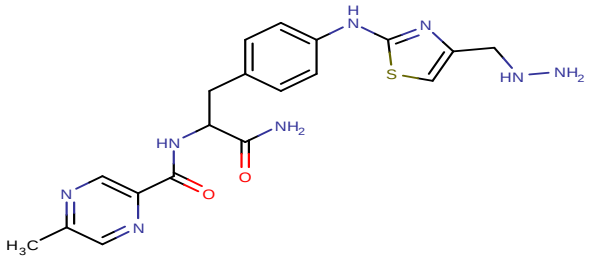
SB1-15		**0.336 ± 0.07**
SB1-16		**0.732 ± 0.09**
SB1-19		**1.210 ± 0.11**
SB1-20		**0.662 ± 0.12**

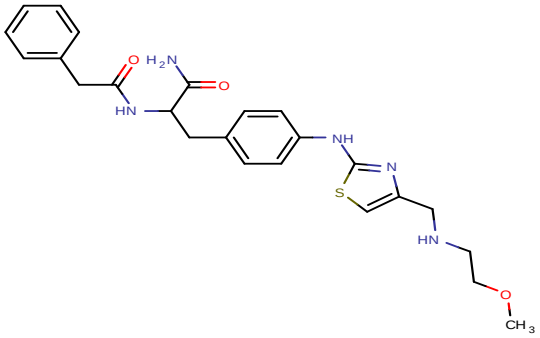
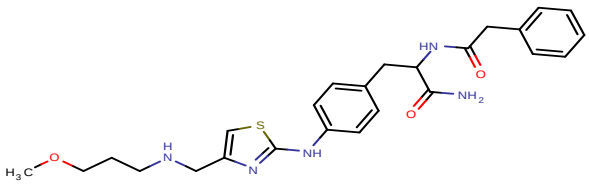
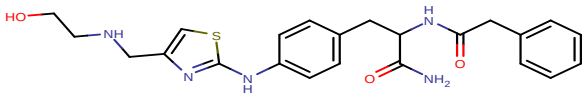
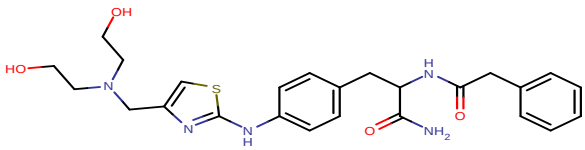
SB1-21		**0.551 ± 0.07**
SB1-22		**0.759 ± 0.10**
SB1-23		**0.489 ± 0.07**
SB1-25		**0.297 ± 0.05**

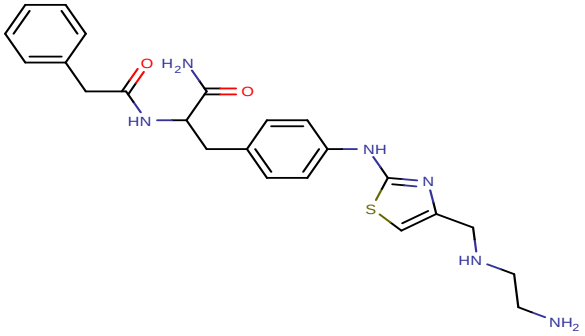
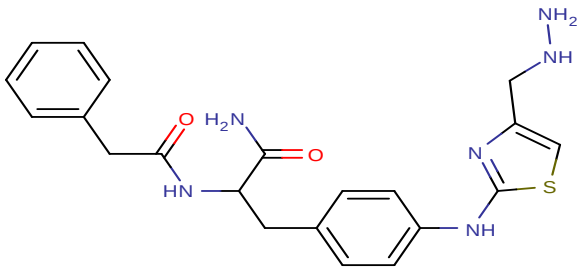
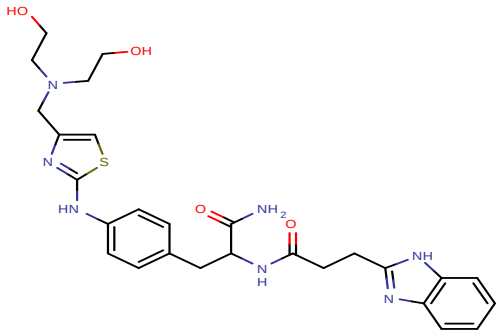
SB1-27		**0.827 ± 0.05**
SB1-29		**0.460 ± 0.05**
SB1-32		**0.807 ± 0.07**
SB1-37		**0.349 ± 0.05**

SB1-41		**0.743 ± 0.09**
SB1-42		**0.487 ± 0.04**
SB1-43		**0.680 ± 0.07**
SB1-44		**0.746 ± 0.09**

SB1-45		**1.103 ± 0.17**
SB1-46		**0.310 ± 0.09**
SB1-49		**0.747 ± 0.07**
SB1-50		**0.748 ± 0.10**

SB1-51		**>2.5**
SB1-52		**0.499 ± 0.06**
SB1-53		**0.684 ± 0.04**
SB1-54		**0.416 ± 0.04**

SB1-55		**0.555 ± 0.06**
SB1-56		**0.513 ± 0.05**
SB1-57		**0.985 ± 0.15**
SB1-58		**0.655 ± 0.03**

SB1-59		**0.531 ± 0.07**
SB1-60		**0.524 ± 0.06**
SB1-64		**0.267 ± 0.05**