

Organic & Biomolecular Chemistry

Antinociceptive Activity of Thiazole-containing Cyclized DAMGO and Leu-(Met) Enkephalin Analogs

Hannah M. Harris^{a†}, Shainnel O. Eans^a, Michelle L. Ganno^b, Jennifer C. Davis^b, Colette T. Dooley^b,
Jay P. McLaughlin^a and Adel Nefzi^{* b}

Supporting Information

Page 2: ¹H and ¹³C NMR data

Pages 3-20: LC-MS and structures of all cyclic peptides

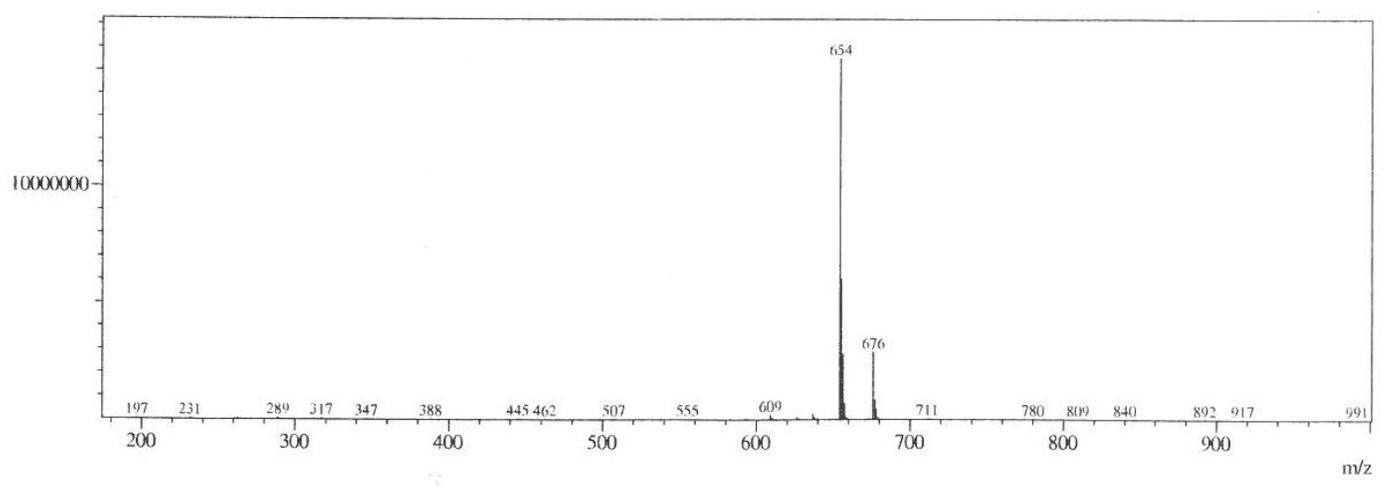
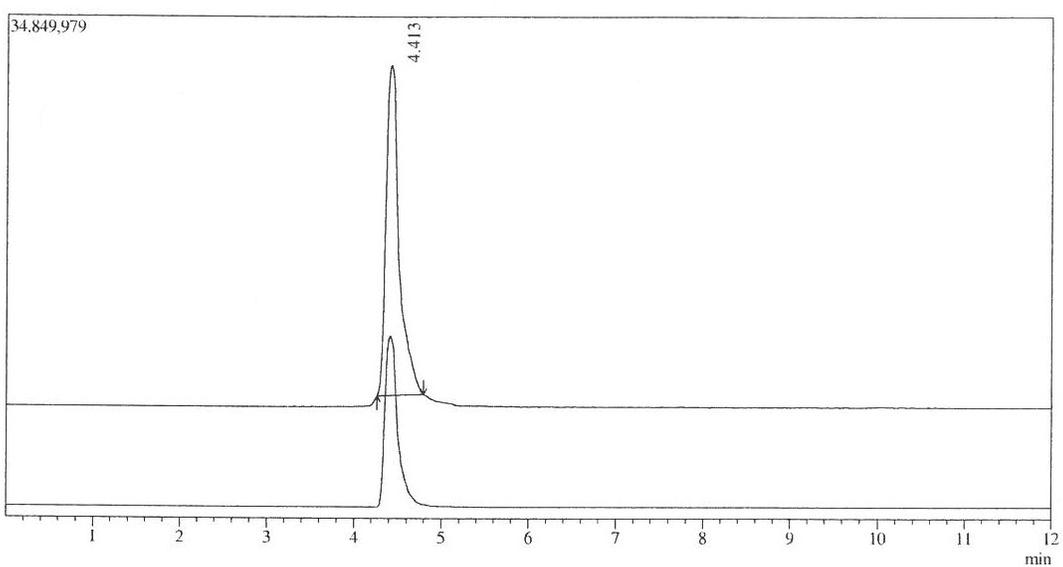
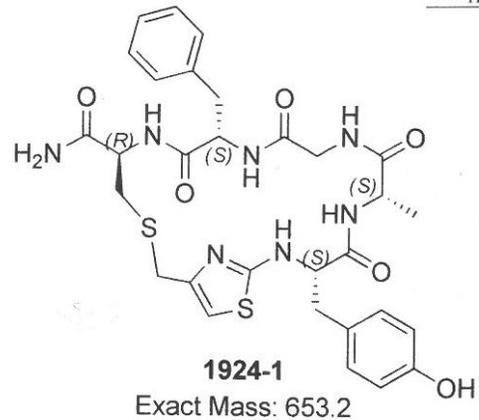
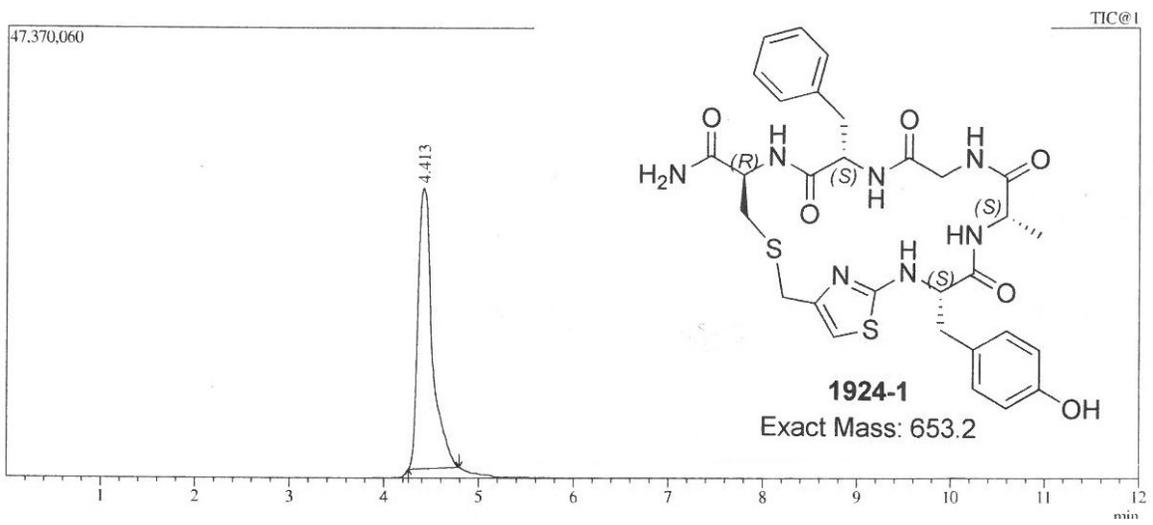
Pages 21-25: NMR spectra and data of cyclic peptides 1936-9 and 1924-10

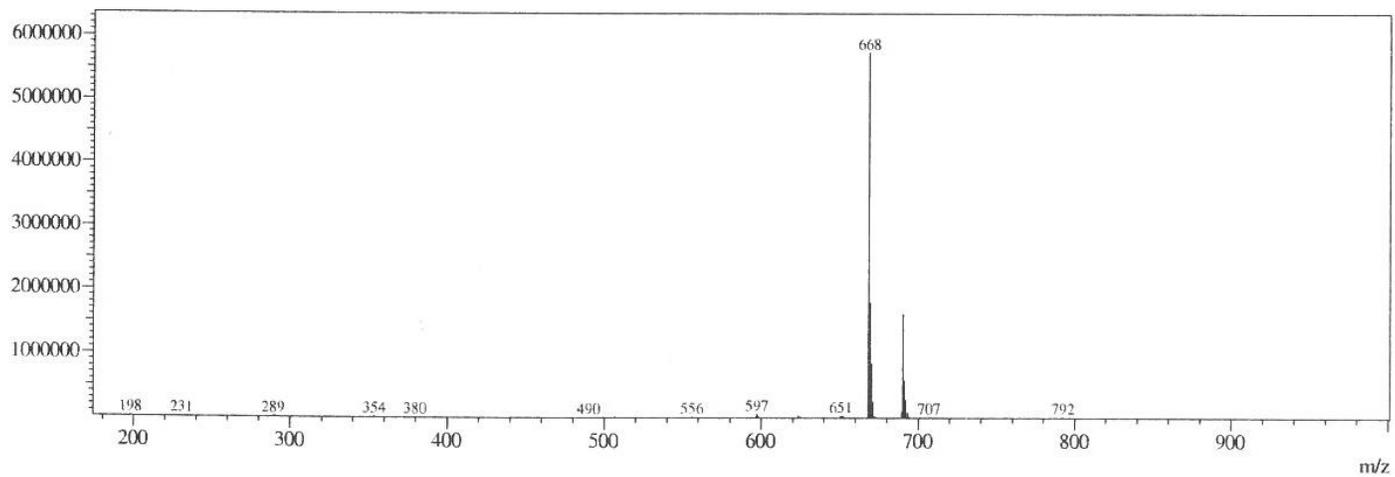
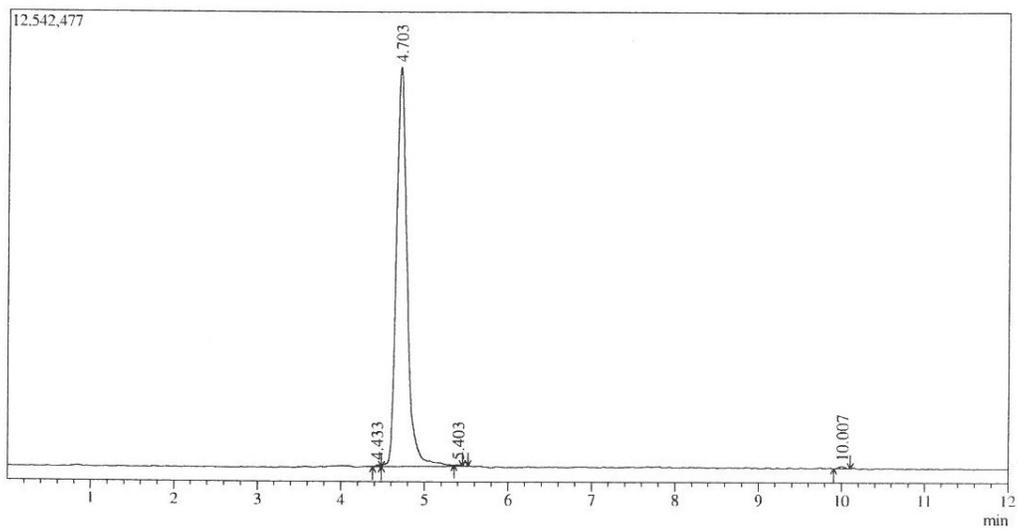
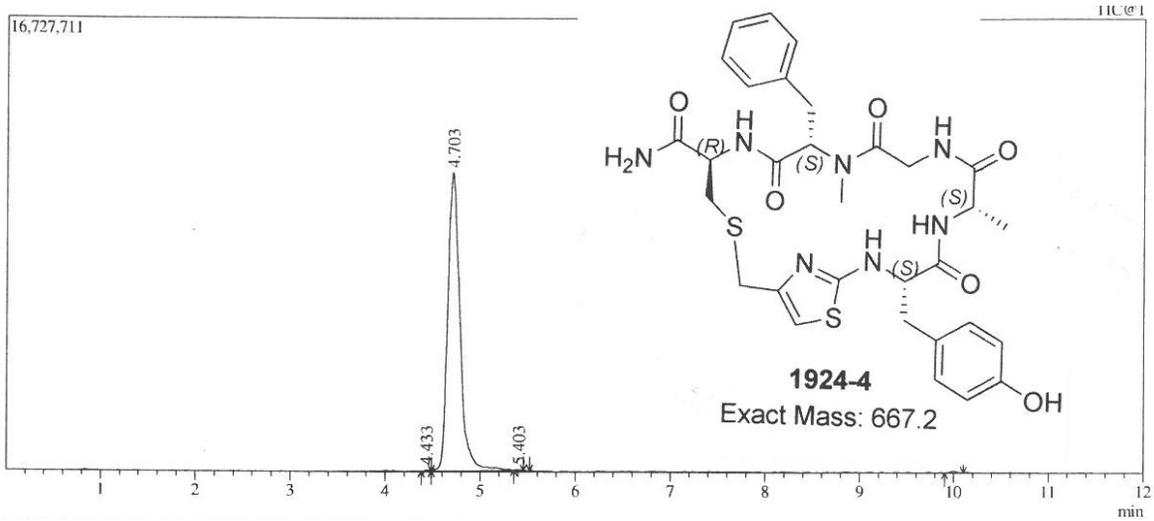
Page 26: Comparative chemistry space: Approximate three-dimensional chemical space of five cyclic peptides

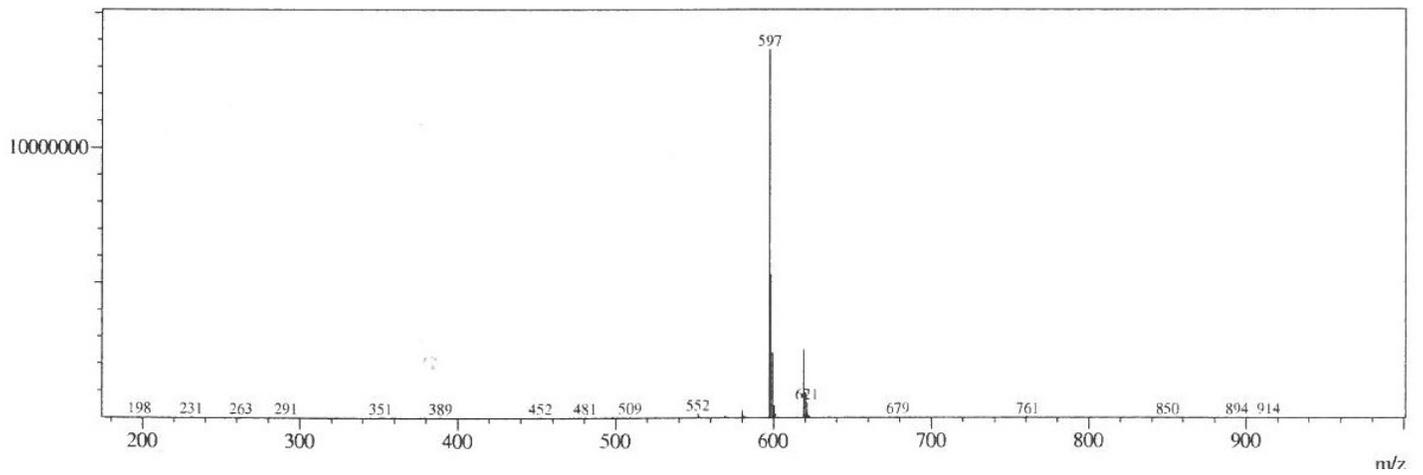
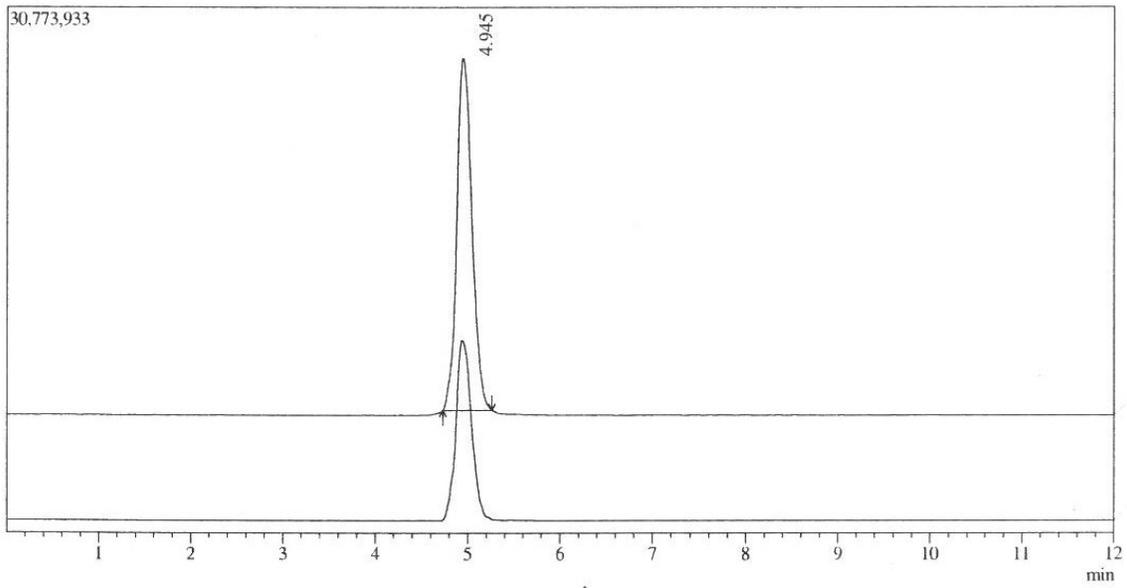
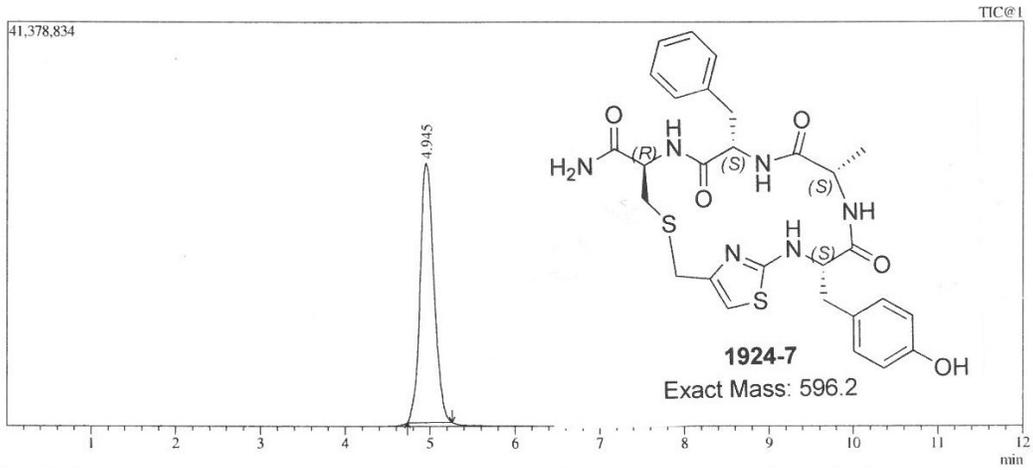
Physical characterization data of representative compounds

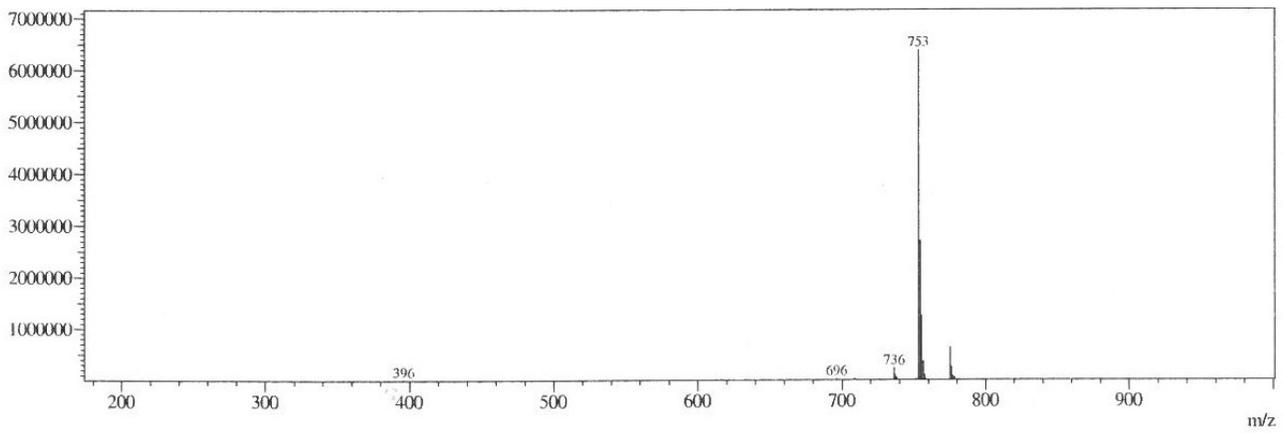
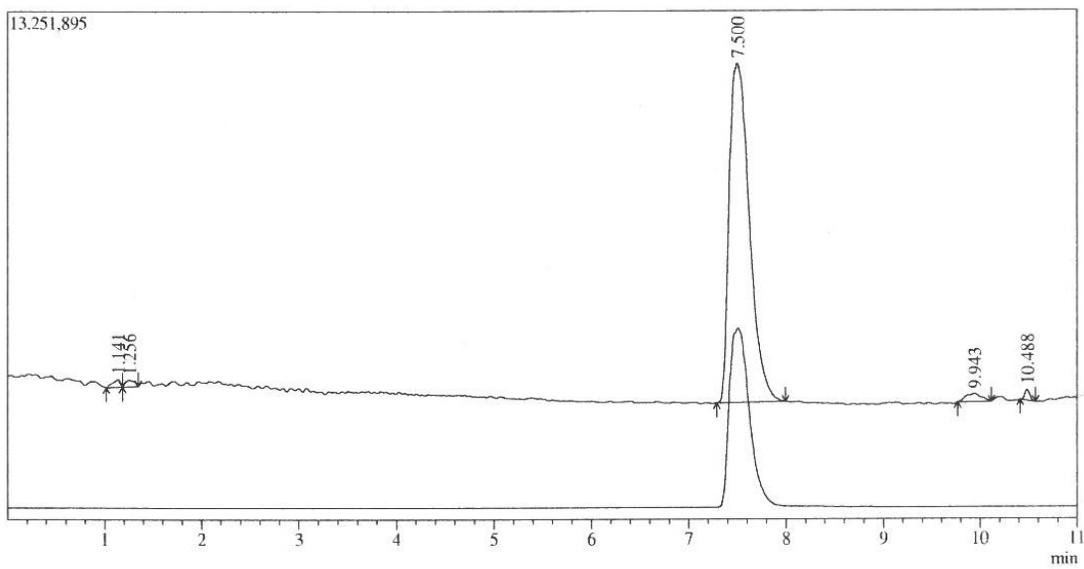
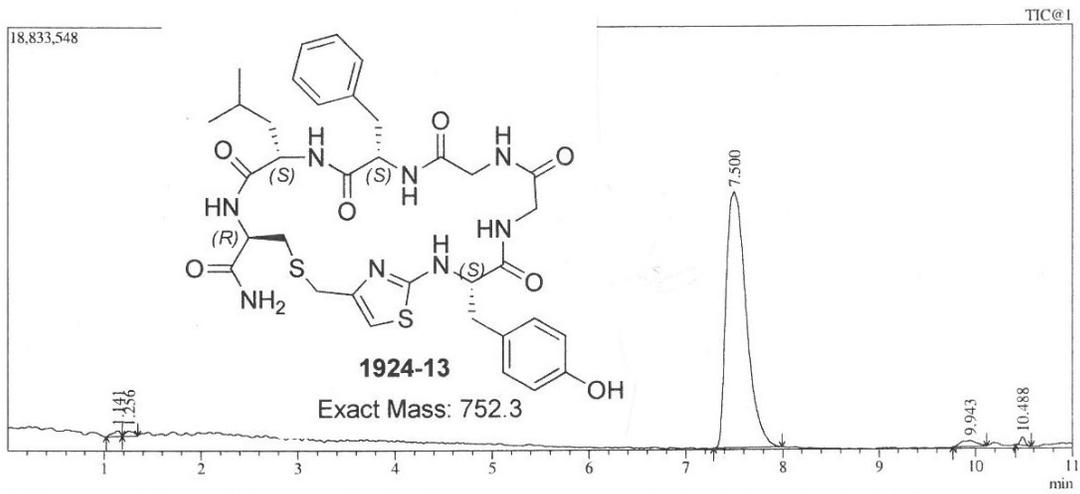
Compound 1924-10: ¹H NMR (400 MHz, DMSO-d₆) δppm 9.1 (s, 1H) 7.09, 7.81 (t, J= 8.96 Hz, 1H), 7.47 (d, J= 2.44 Hz, 1H), 7.24 (m, 2H), 7.13 (m, 2H), 6.95 (d, J= 8.24 Hz, 2H), 6.58 (d, J= 8.16 Hz, 1H), 6.31 (s, 1H), 5.23 (d, J= 11.56 Hz, 1H), 4.39 (m, 2H), 4.19 (m, 2H), 4.01 (m, 2H), 3.52 (d, J= 14.48 Hz, 1H), 3.37 (m, 1H), 3.27 (m, 2H), 3.01 (m, 2H), 2.83 (m, 4H), 2.78 (m, 2H), 2.72 (m, 2H), 2.57 (s, 3H), 0.27 (d, J= 6.4 Hz, 3H). ¹³C NMR (100 MHz, DMSO-d₆) δppm 173.59, 172.89, 172.60, 167.54, 156.48, 150.18, 138.44, 130.39, 129.82, 129.00, 127.72, 126.99, 115.57, 103.68, 62.32, 62.09, 56.96, 42.32, 37.04, 33.92, 33.10, 29.86, 16.57. MS (ESI): m/z calcd for C₂₉H₃₄N₆O₅S₂ [M + H]⁺ : 611.2, found: 611.0.

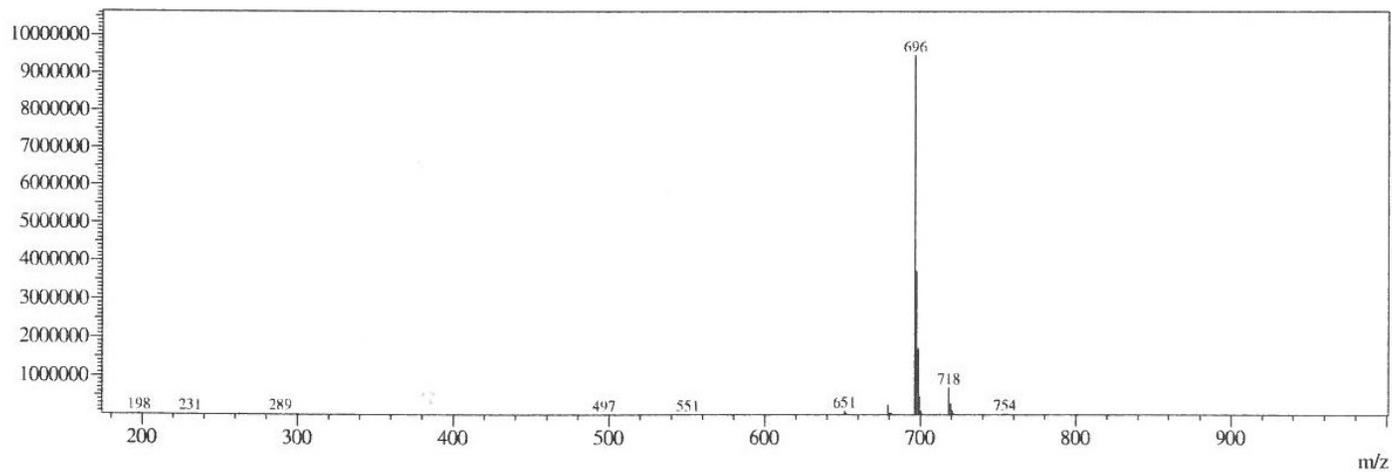
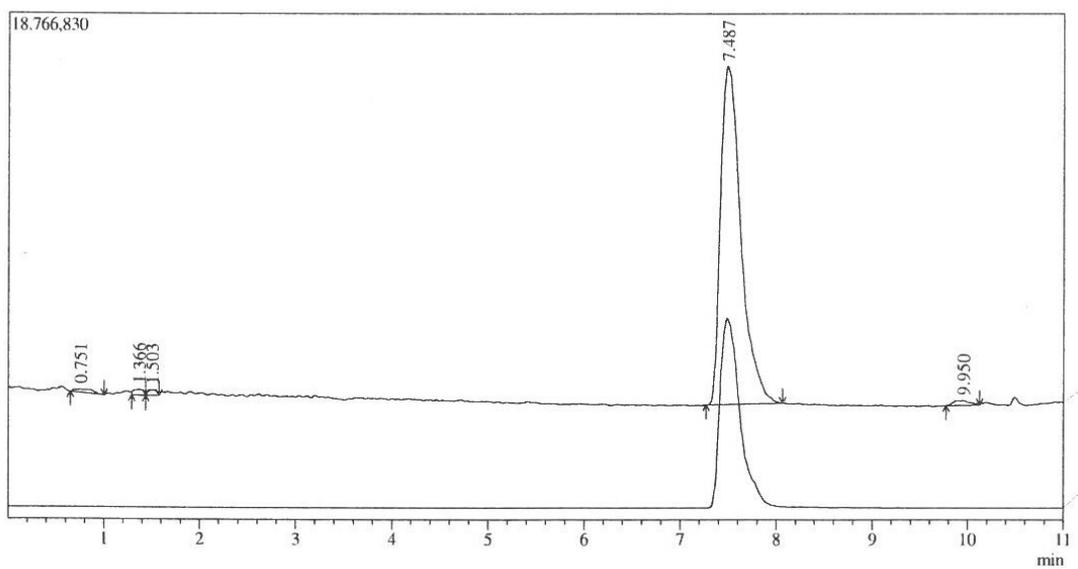
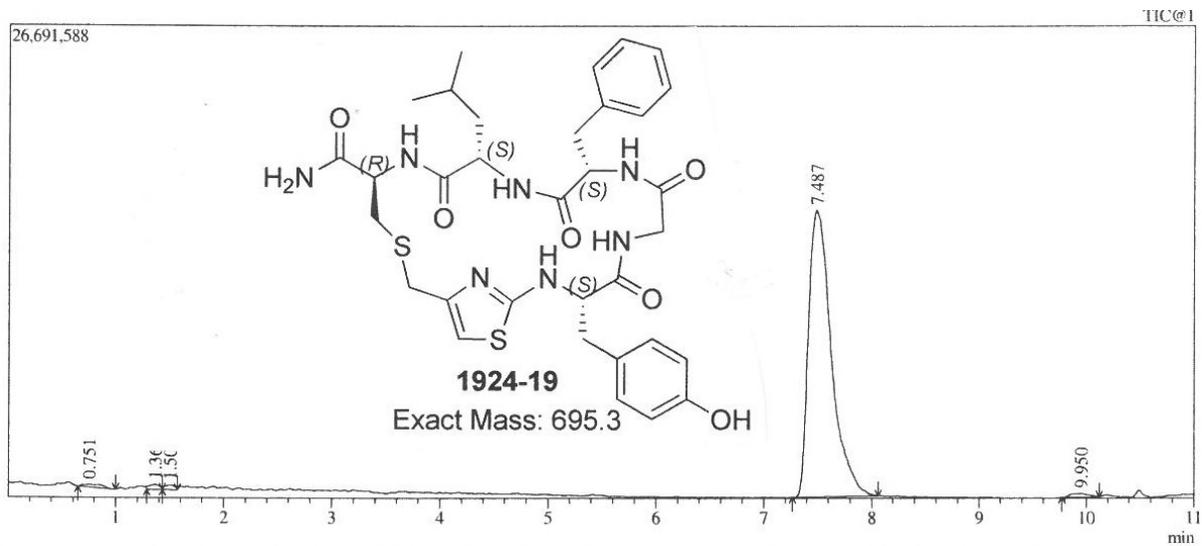
Compound 1936-9: ¹H NMR (400 MHz, DMSO-d₆) δppm 9.08 (s, 1H), 8.23 (d, J= 7.72 Hz, 1H), 7.78 (d, J= 6.72 Hz, 1H), 7.69 (d, J= 7.60 Hz, 1H), 7.09 (m, 3H), 7.02 (m, 2H), 6.56 (d, J= 6.84 Hz, 2H), 6.28 (s, 1H), 4.42 (m, 1H), 4.25 (m, 1H), 4.22 (m, 1H), 4.20 (d, J=6.40 Hz, 1H), 4.12 (d, J= 8.28 Hz, 1H), 3.90 (d, J=6.40 Hz, 1H), 3.43 (bs, 1H), 2.92 (m, 2H), 2.87 (m, 2H), 2.75 (m, 2H), 2.72 (m, 2H), 1.52 (m, 2H), 1.39 (t, J=6.48 Hz, 3H), 0.77 (dd, J= 20.00 Hz, J=5.20 Hz, 3H). ¹³C NMR (100 MHz, DMSO-d₆) δppm 172.77, 171.75, 171.67, 169.96, 167.88, 155.79, 148.99, 137.76, 137.48, 129.73, 129.05, 128.85, 114.90, 103.42, 61.45, 56.20, 54.55, 54.32, 51.59, 36.83, 36.50, 35.88, 32.68, 30.30, 23.51, 22.03. MS (ESI): m/z calcd for C₃₃H₄₁N₇O₆S₂ [M + H]⁺ : 696.3, found: 696.0.

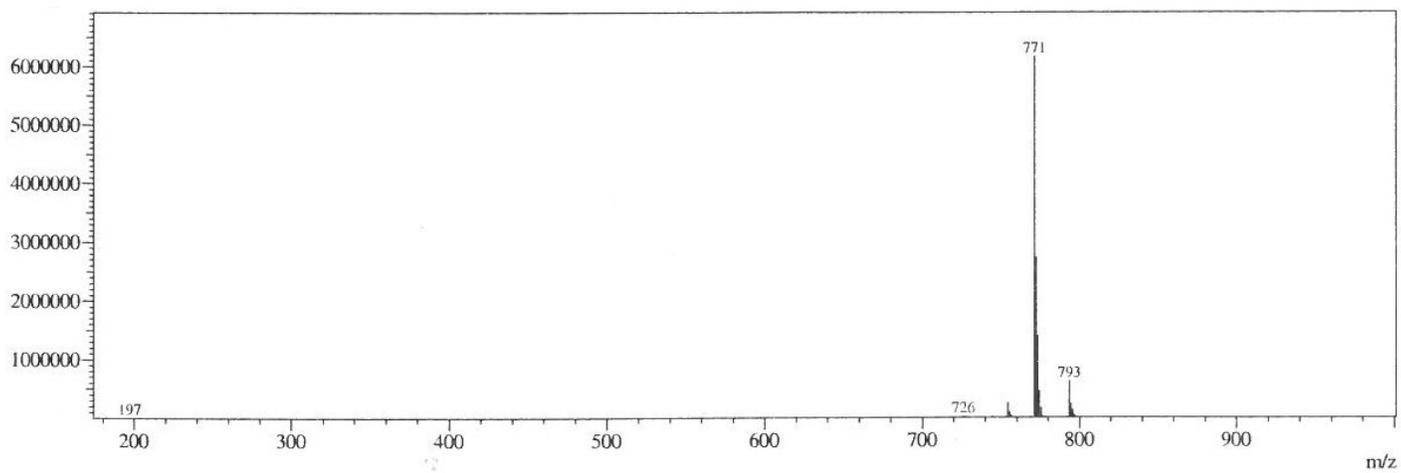
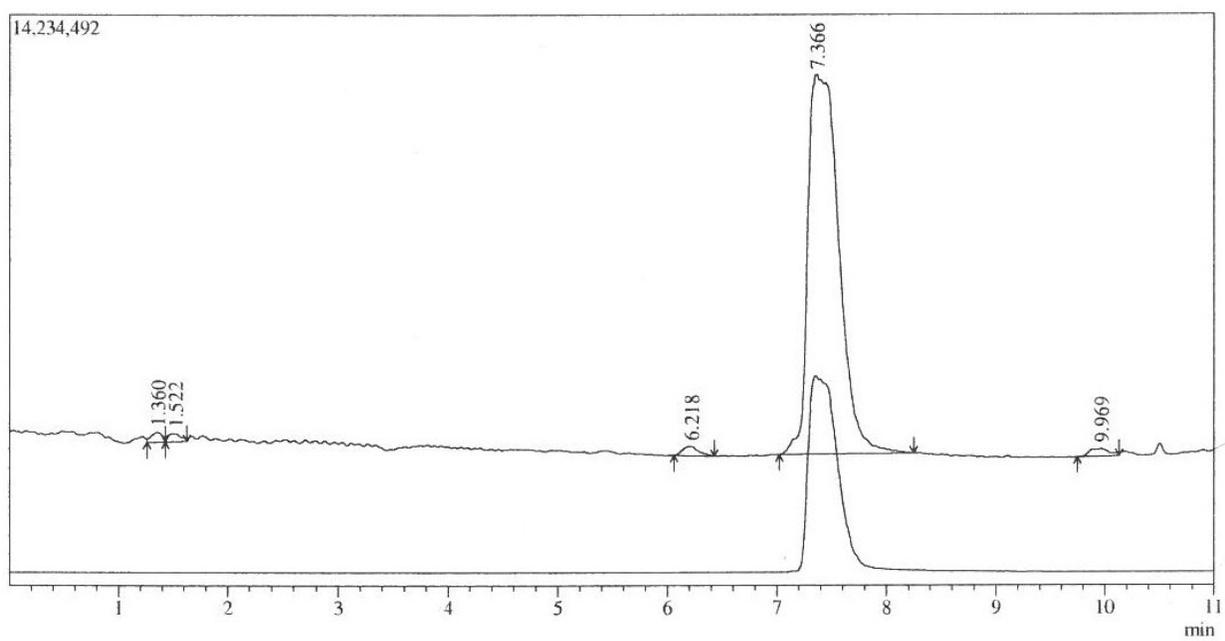
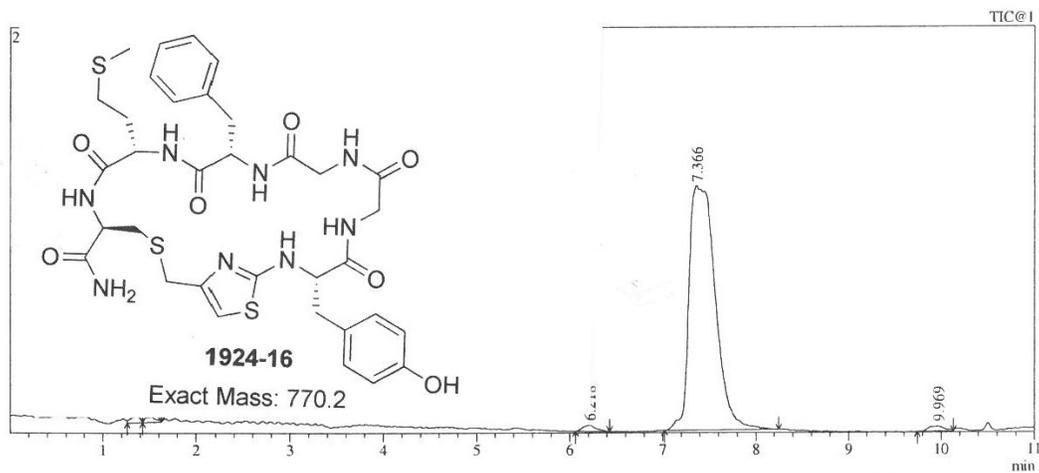


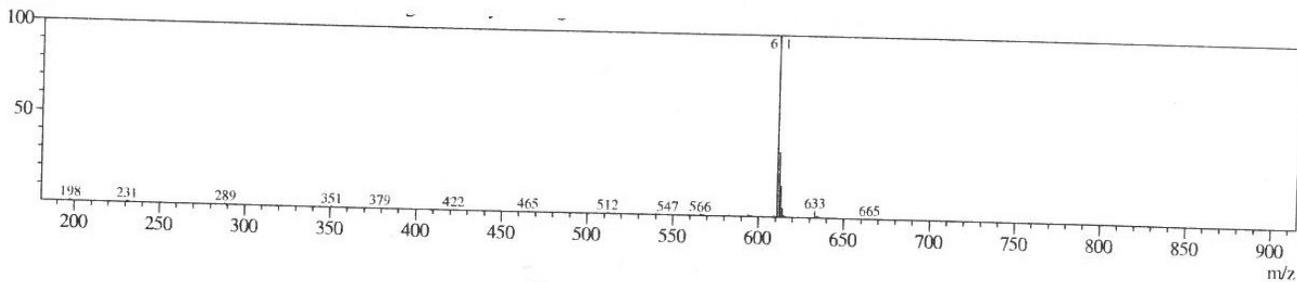
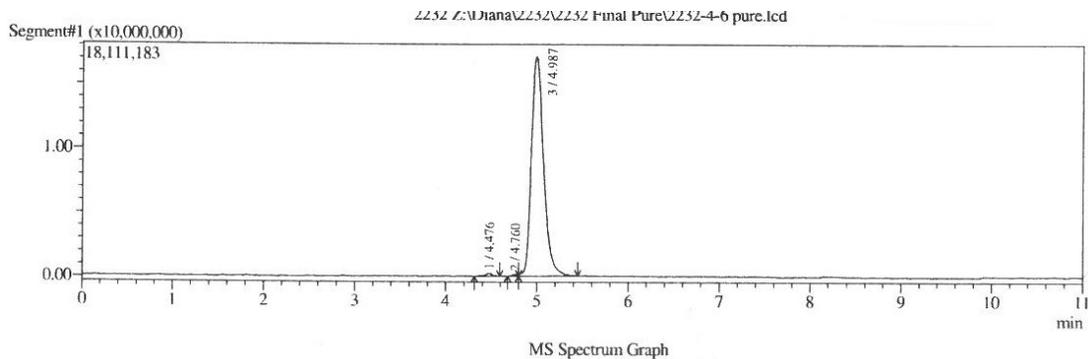
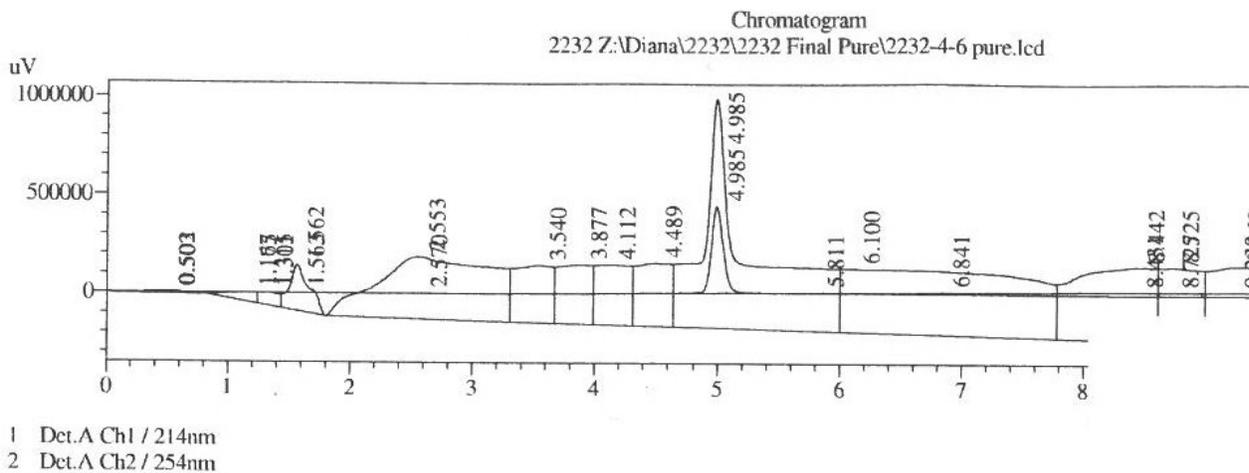
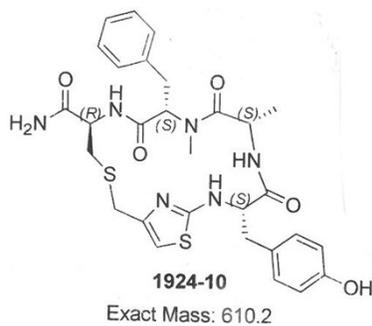


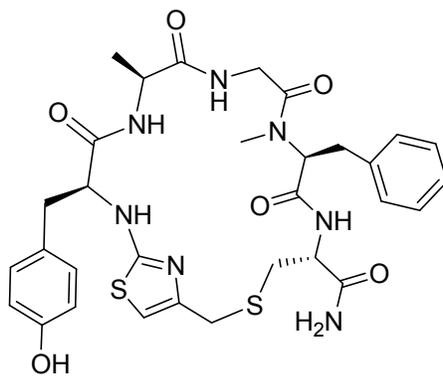




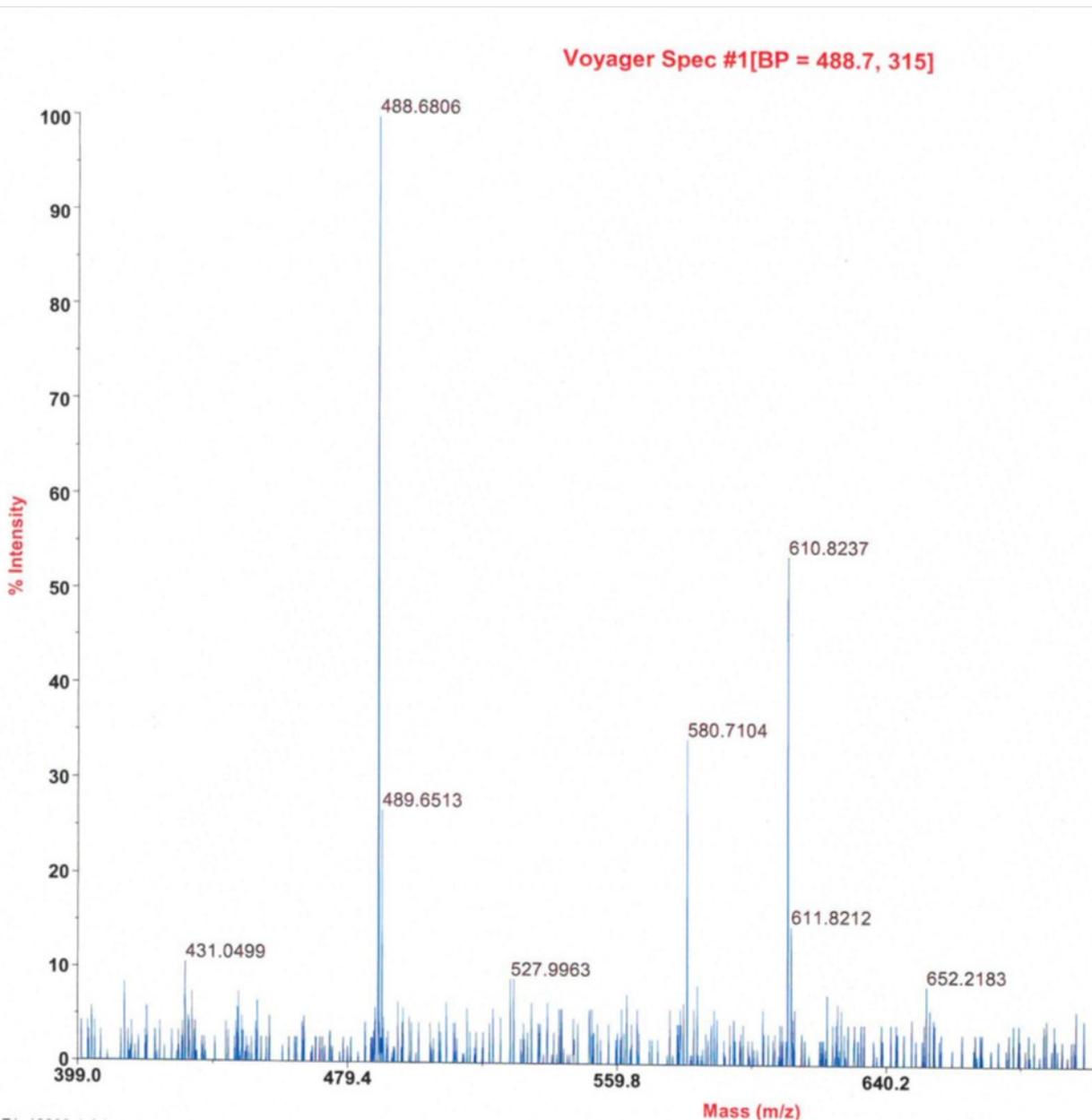


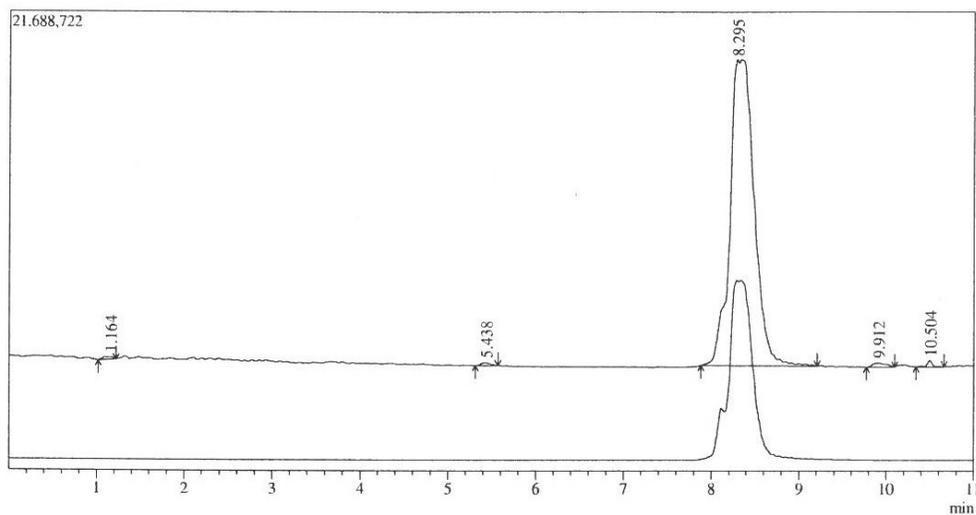
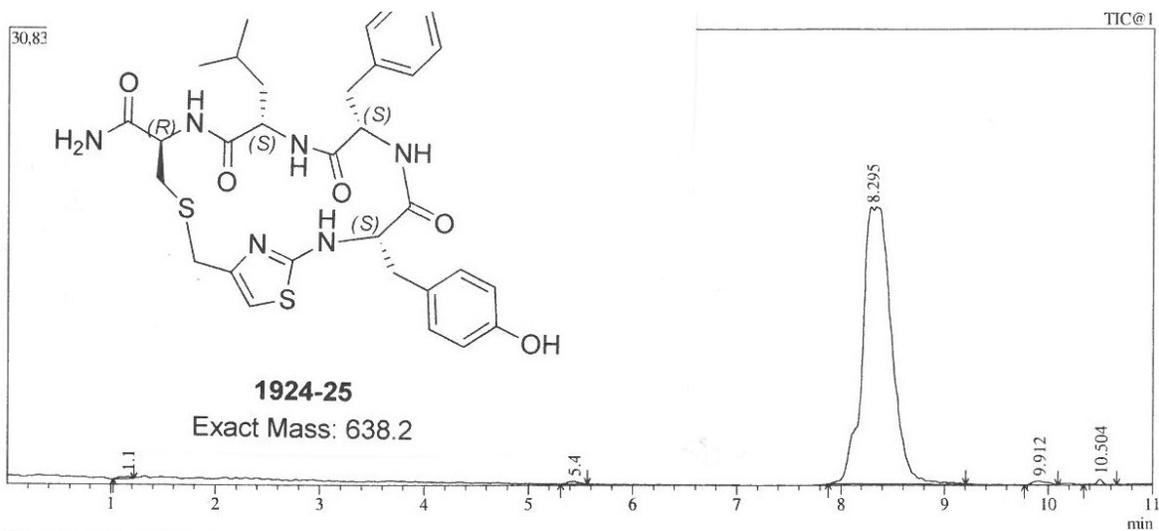




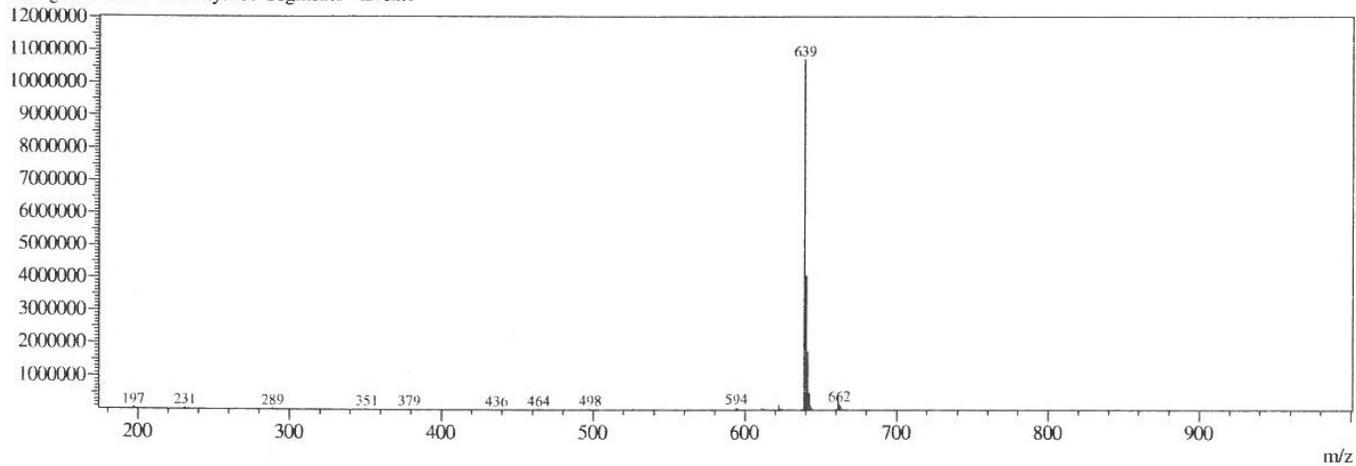


1924-10

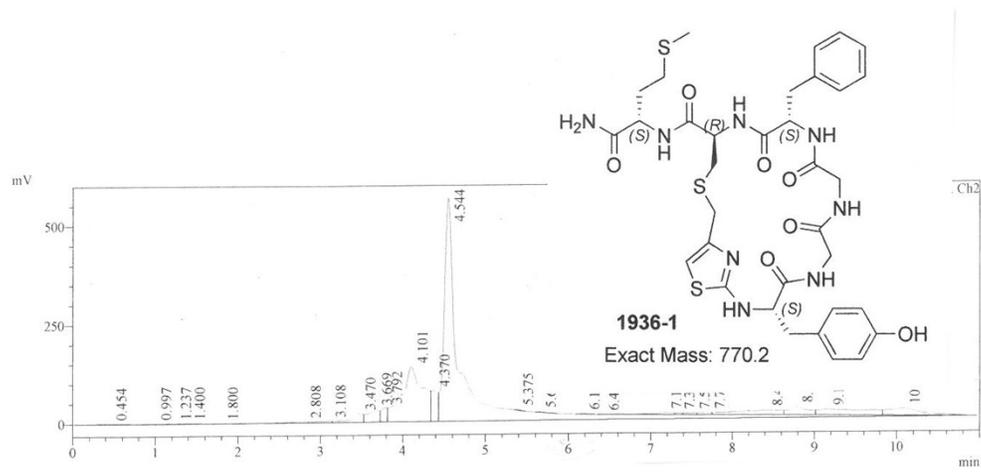
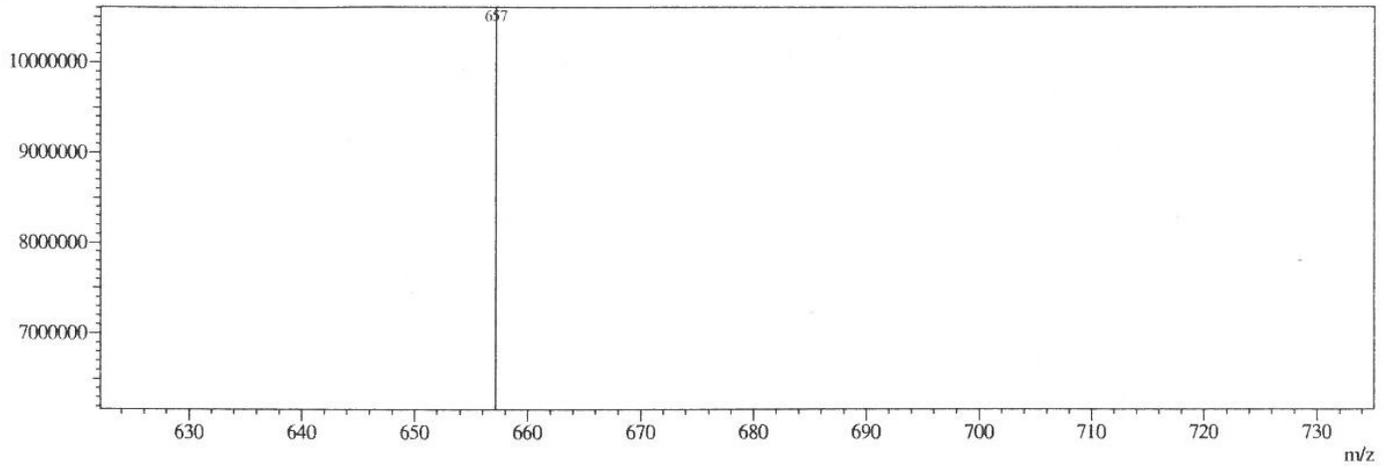




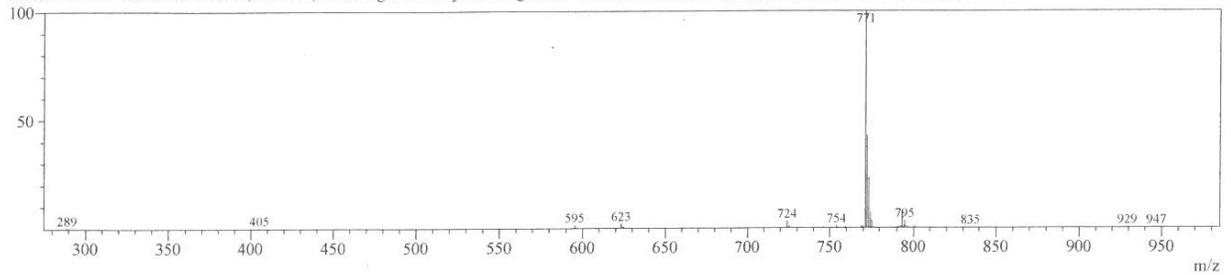
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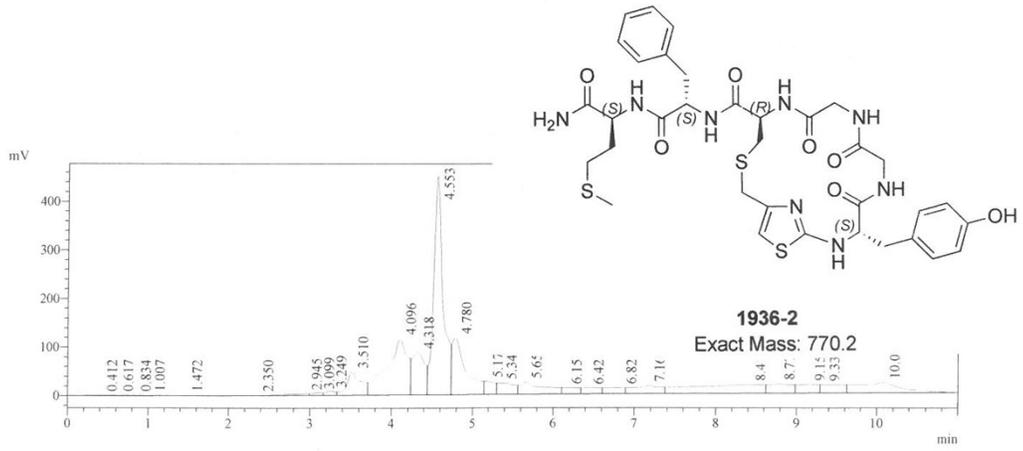


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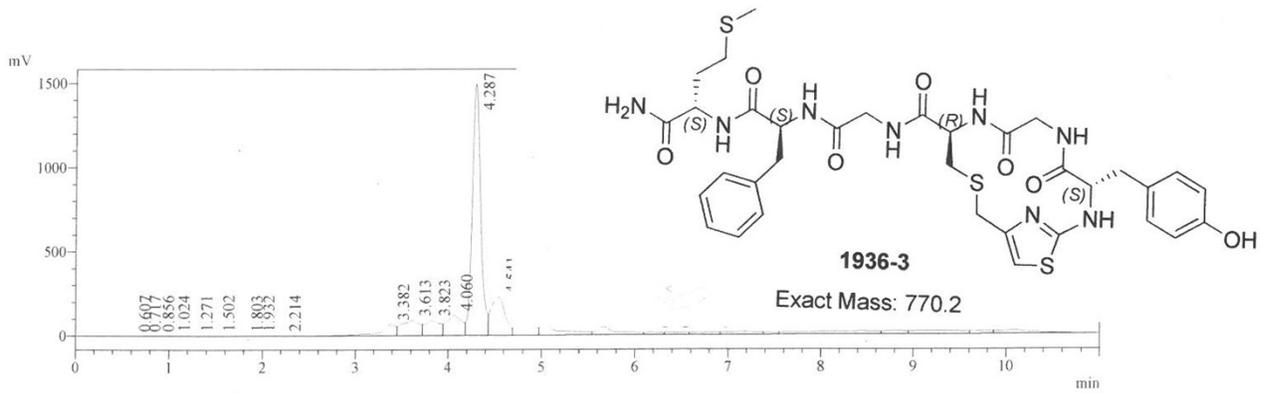
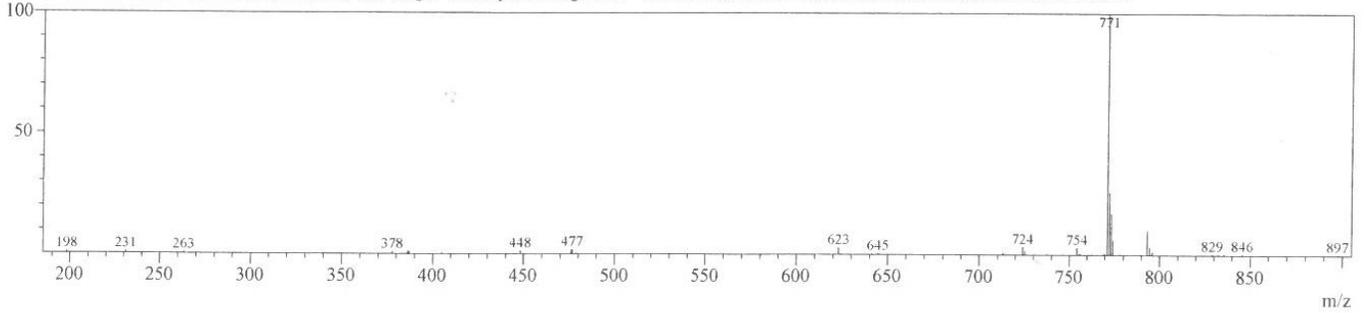


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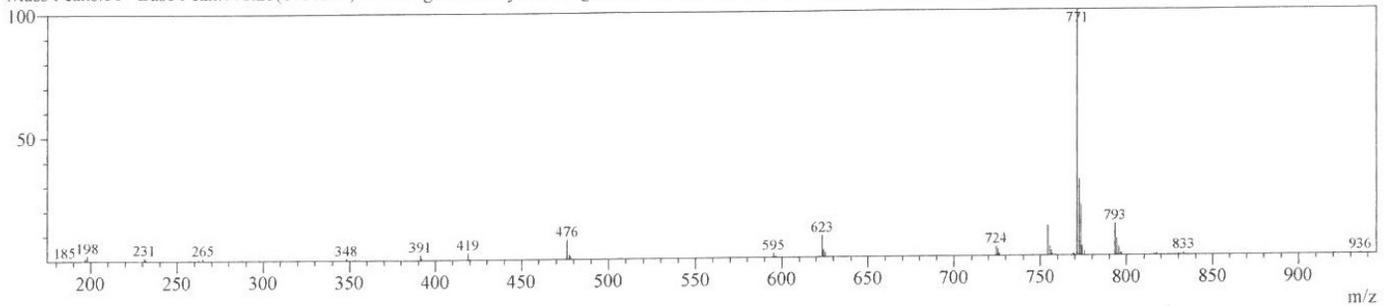


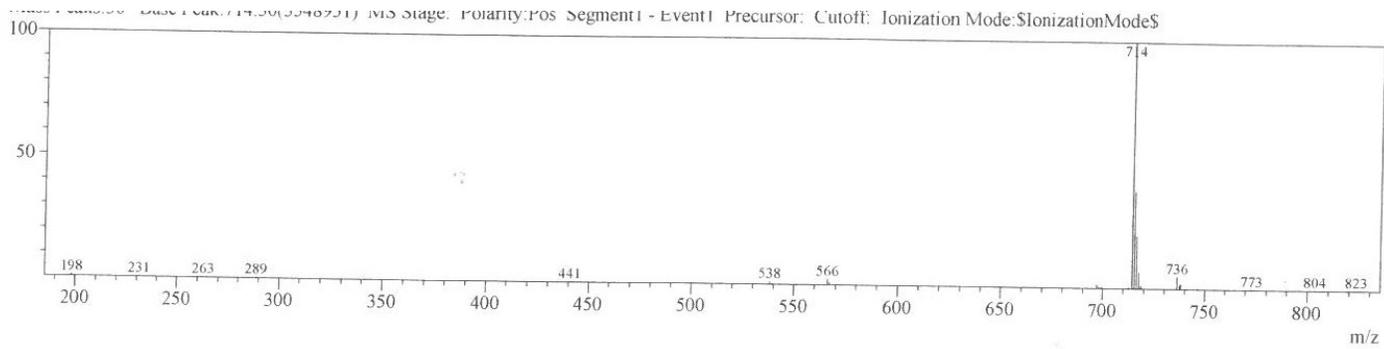
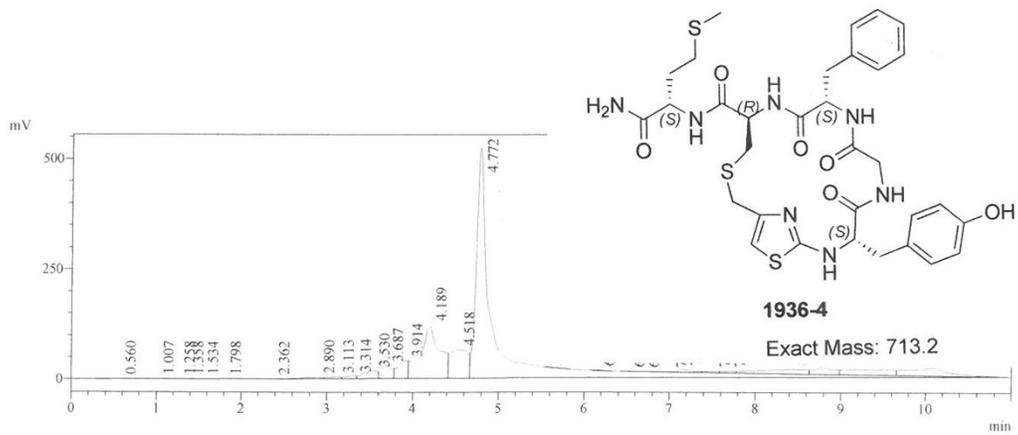


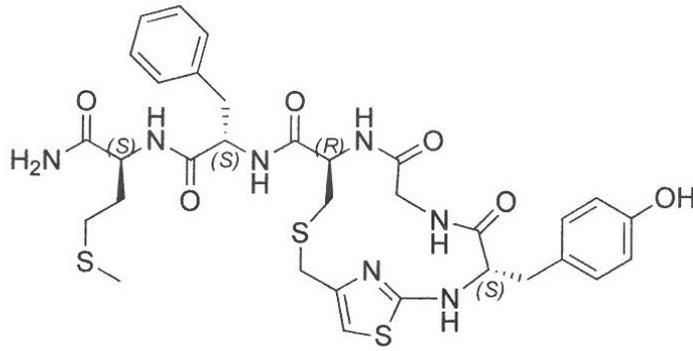
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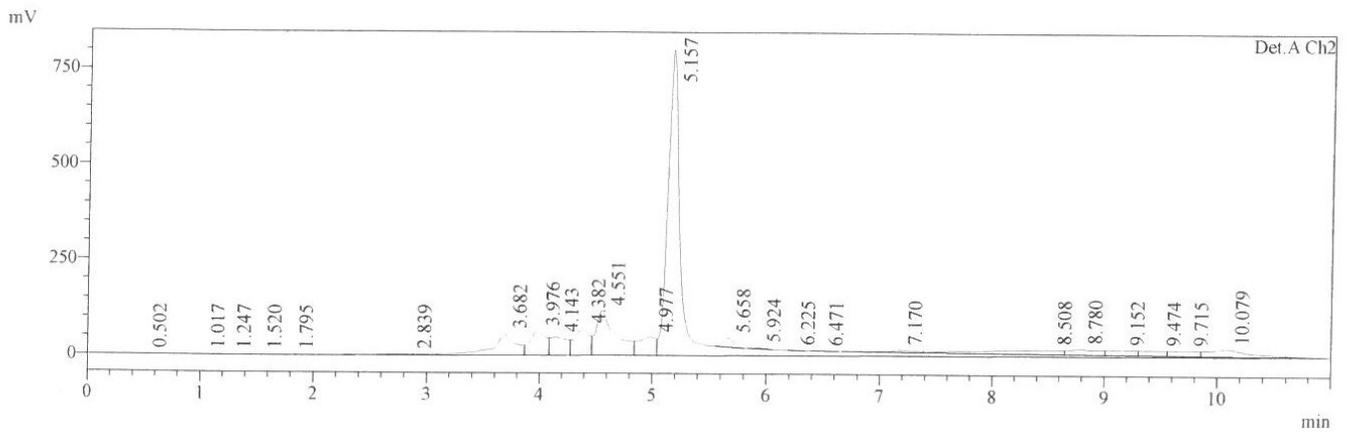






1936-5

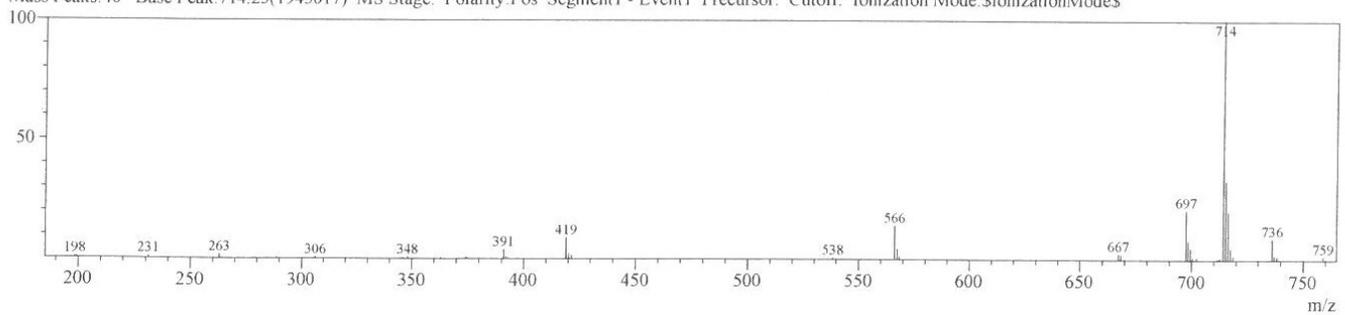
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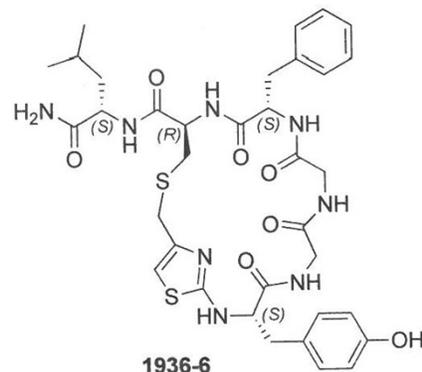
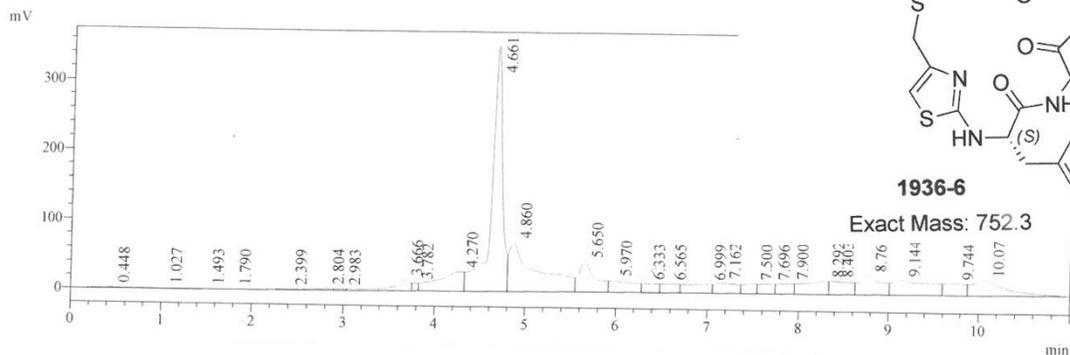


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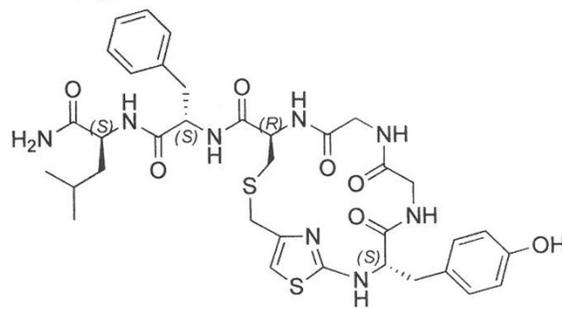
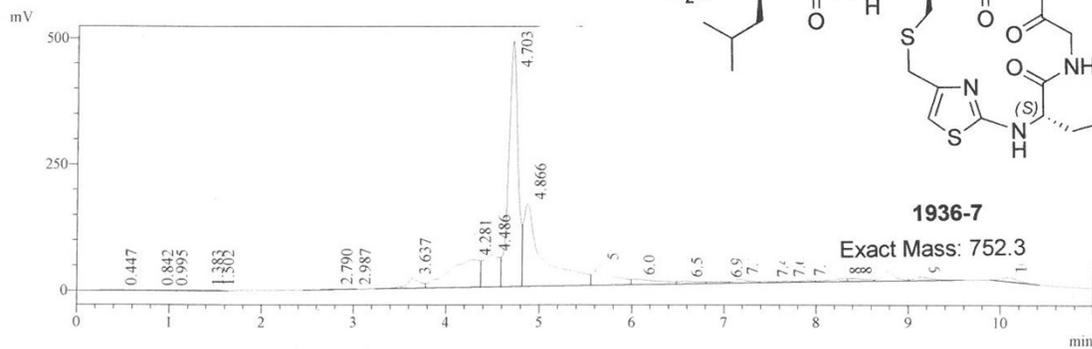
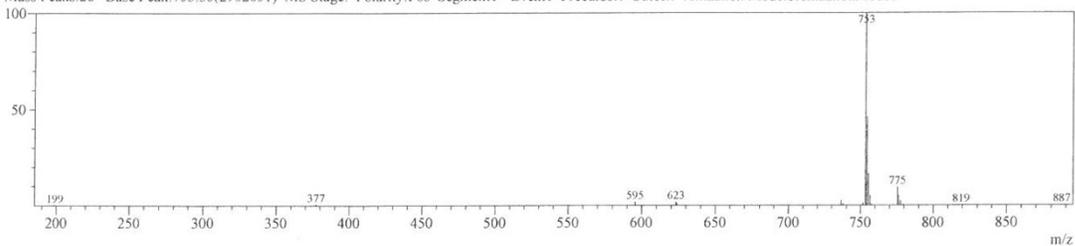




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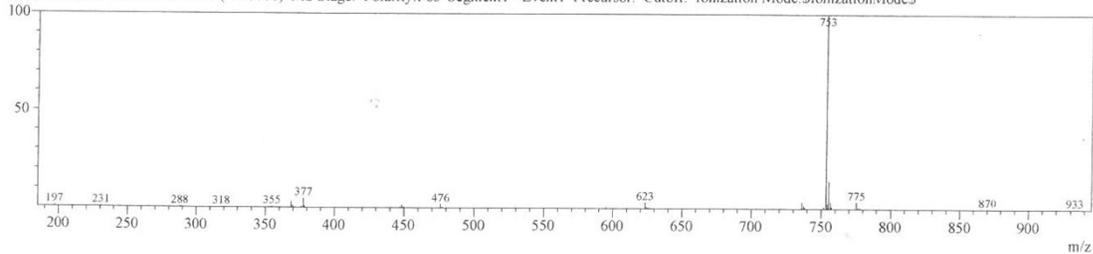
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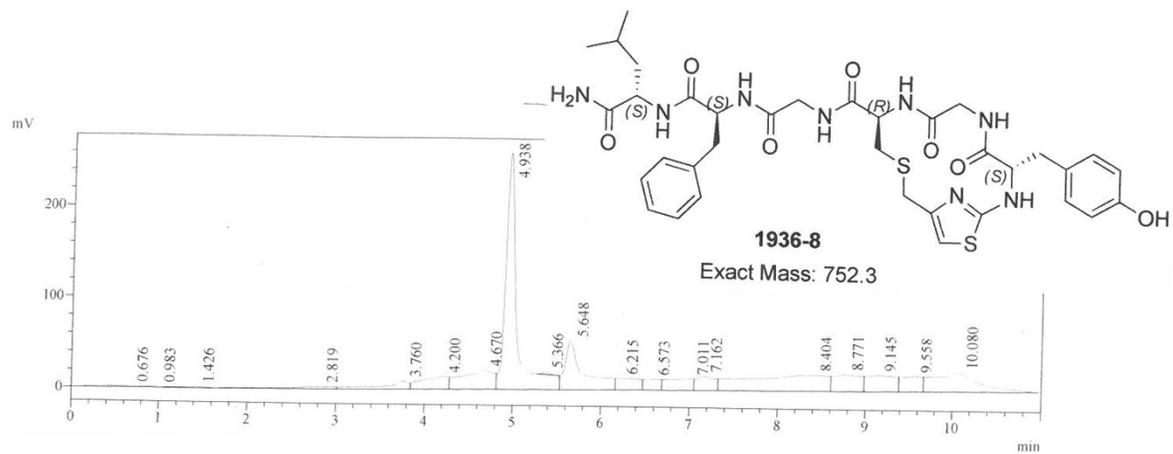


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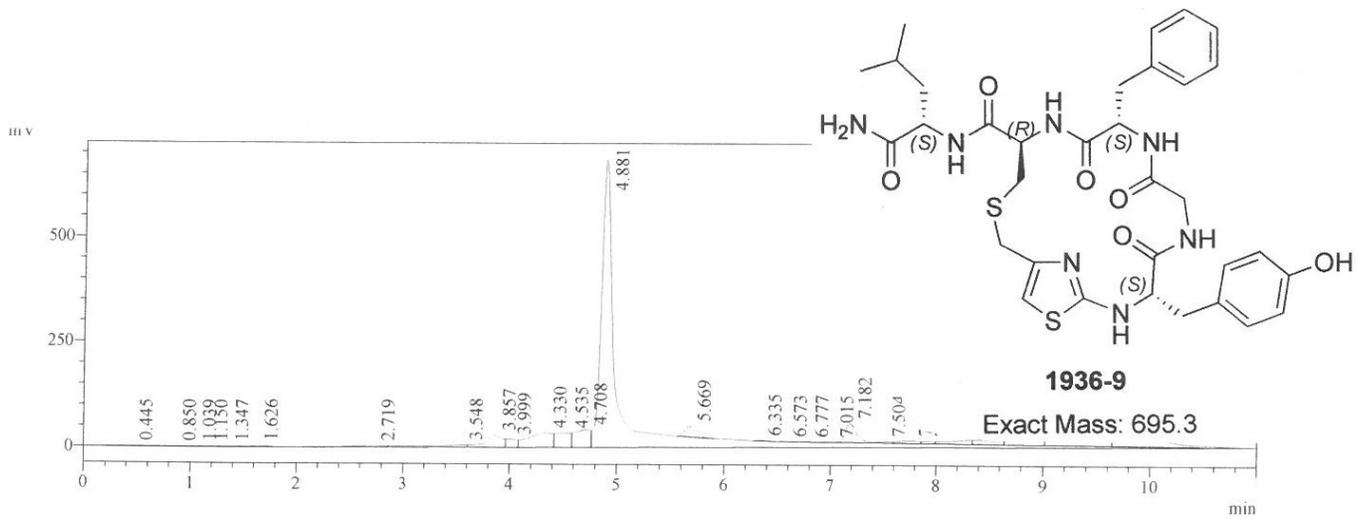
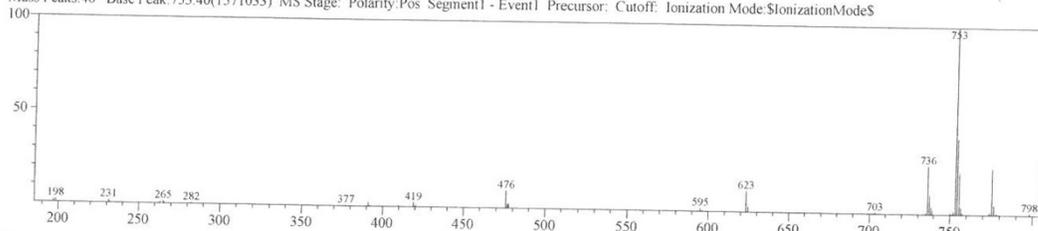




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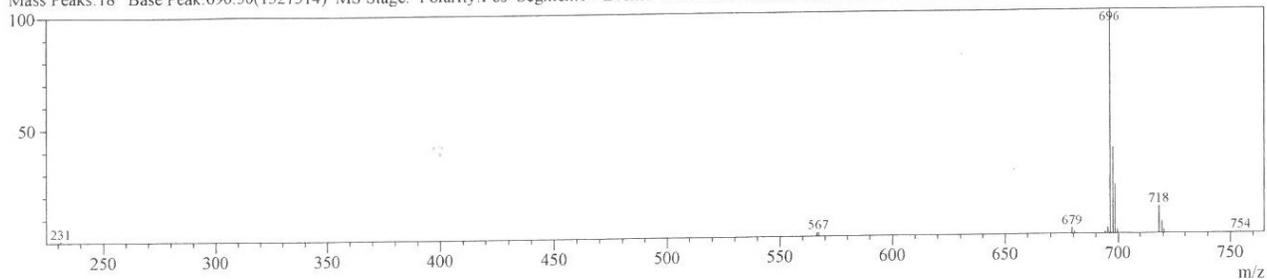
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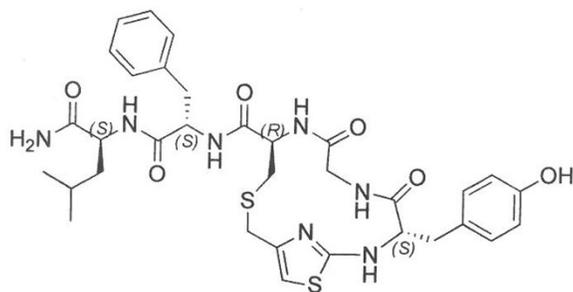


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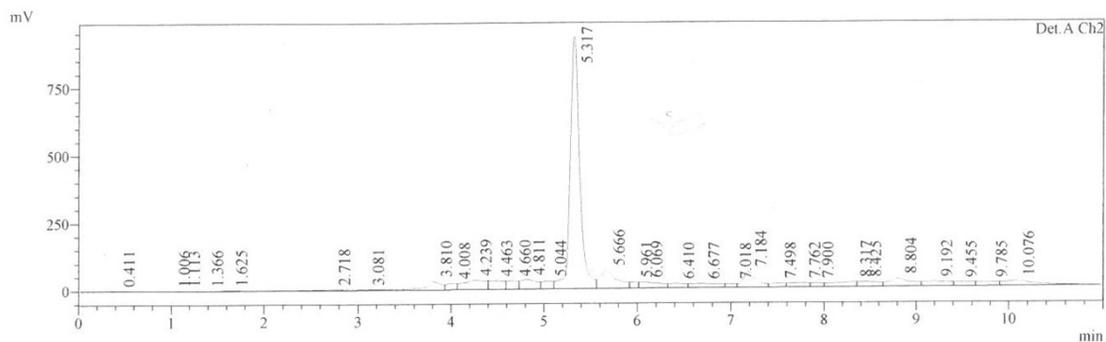
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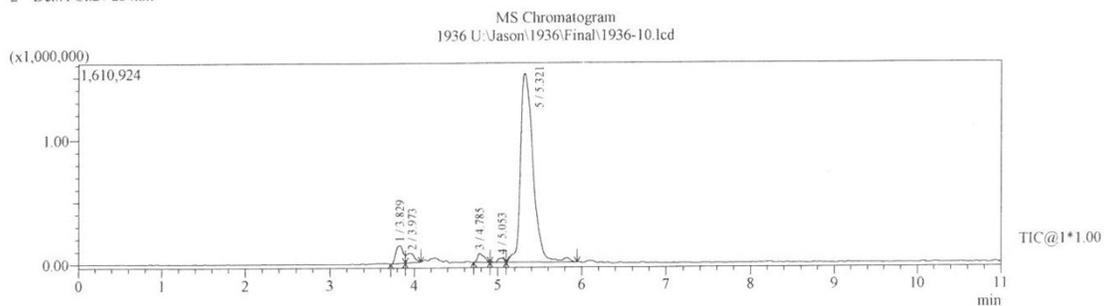


1936-10

Exact Mass: 695.3



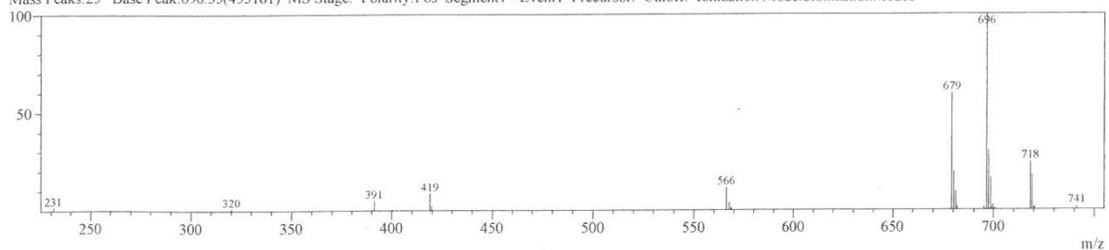
1 Det. A Ch1 / 214nm
2 Det. A Ch2 / 254nm



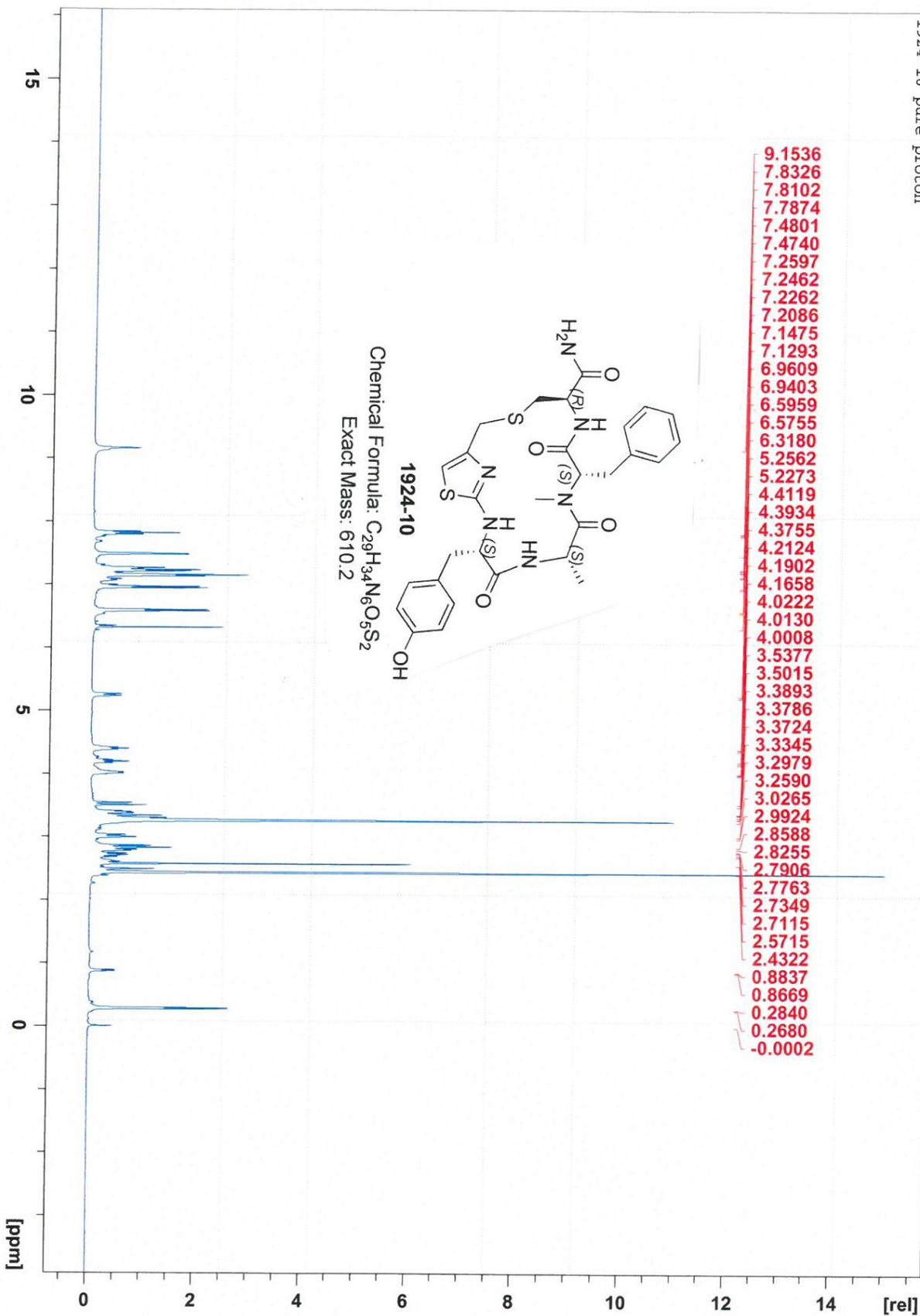
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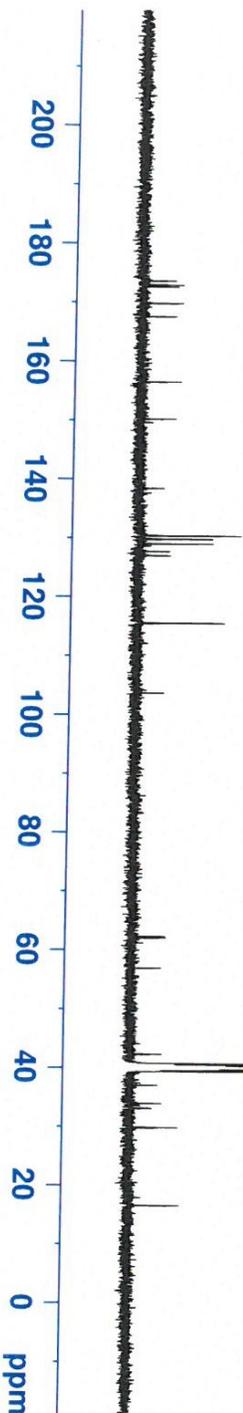
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Feb28-2018-jdavis 10 1 H:jdavis
1924-10 pure proton



1924-10 pure C13



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 PROCNO 1

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 PROBHD 5 mm PABBO BB/
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 SWH 24038.461 Hz
 FIDRES 0.366798 Hz
 AQ 1.3631488 sec
 RG 208.24
 DE 20.800 usec
 TE 299.2 K
 D1 2.00000000 sec
 D11 0.03000000 sec
 TD0 1

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 NUC1 13C
 P1 10.00 usec
 PLW1 64.00000000 W

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 NUC2 1H
 CPDPRG12 waltz16
 PCPD2 90.00 usec
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 PLW12 0.35802001 W
 PLW13 0.289999999 W

F2 - Processing parameters
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1924-10 pure C13 DEPT135



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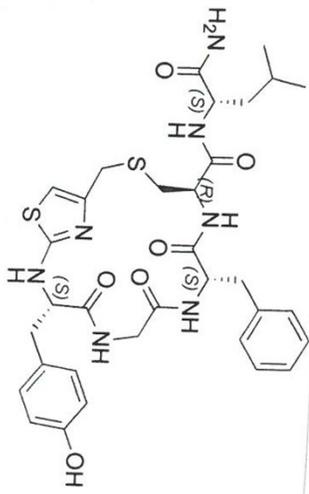
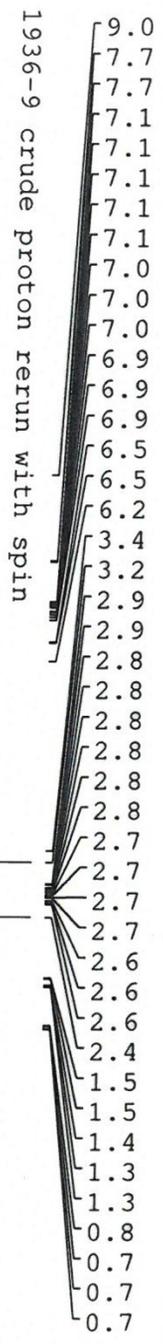
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 FIDRES 0.246110 Hz
 AQ 2.0316160 sec
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 TE 298.3 K
 CNST2 145.0000000
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 D2 0.00344828 sec
 D12 0.00002000 sec
 ID0 1

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 NUC1 13C
 P1 10.00 usec
 P13 2000.00 usec
 PLW0 0 W
 PLW1 64.000000000 W
 SPNAM[5] Crp60comp.4
 SFOALS 0.500
 SFOFFS5 0 Hz
 SPW5 9.77849960 W

CHANNEL f2 =====
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 NUC2 1H
 CPDPRG[2] waltz16
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 PCPD2 90.00 usec
 PLW2 29.000000000 W
 PLW12 0.35802001 W

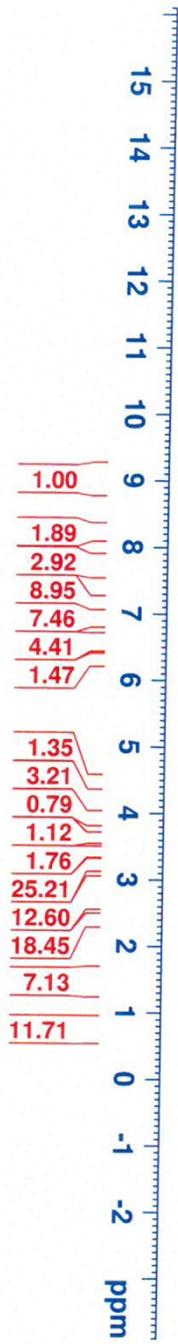
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Chemical Formula: $C_{33}H_{41}N_7O_6S_2$
 Exact Mass: 695.3

1936-9



Current Data Parameters
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 EXPNO 24
 PROCNO 1

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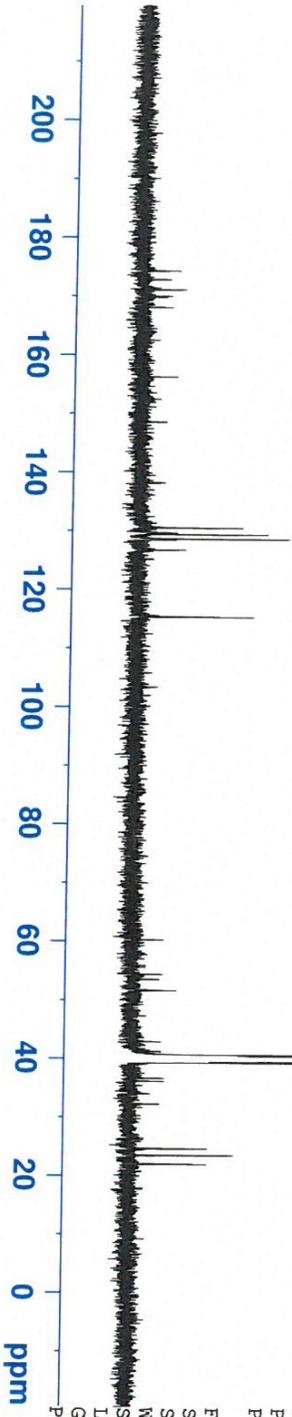
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 GB 0
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1936-9 crude C13 rerun with spin

174.26
172.80
171.07
169.95
168.08
156.23
148.52
130.54
129.62
129.41
128.64
126.76
115.34

60.26
54.37
53.51
51.60
42.89
41.19
40.59
40.38
40.17
39.96
39.75
39.54
39.33
36.64
36.11
32.24
24.61
23.48
21.98



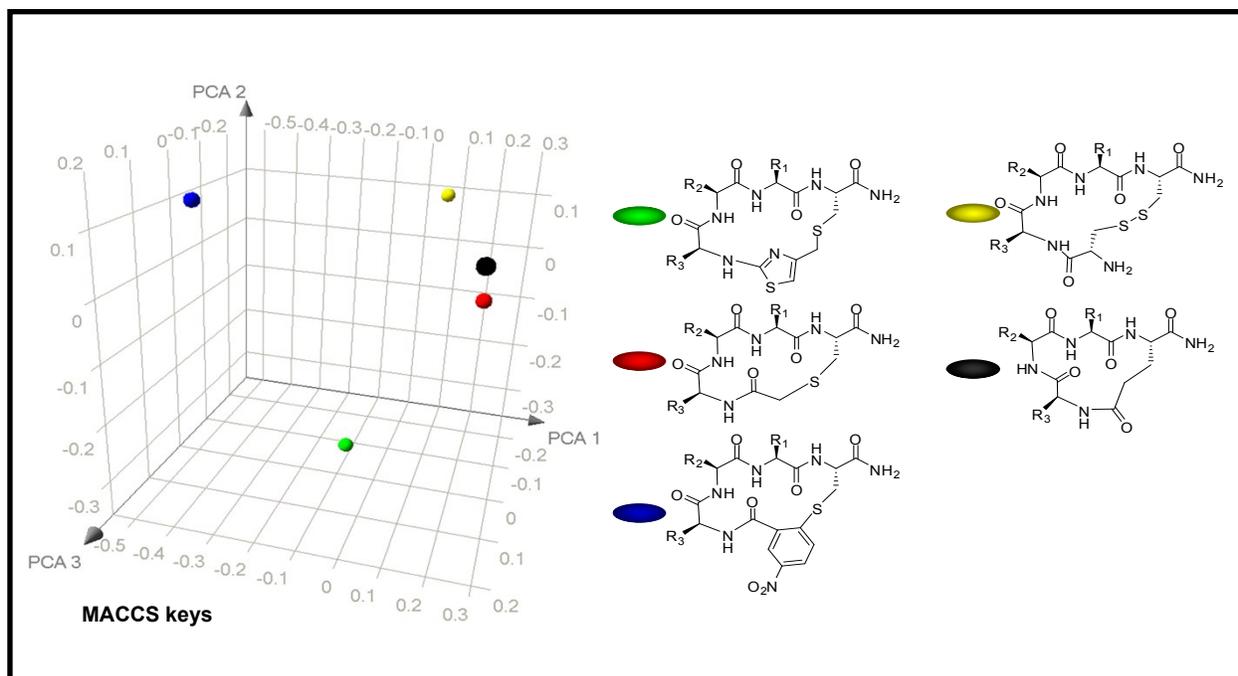
Current Data Parameters
NAME Mar01-2018-jdavis
EXPNO 27
PROCNO 1

F2 - Acquisition Parameters
Date_ 20180301
Time 15.35
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 2048
DS 4
SWH 24038.461 Hz
FIDRES 0.366798 Hz
AQ 1.3631488 sec
RG 208.24
DW 20.800 usec
DE 6.50 usec
TE 299.3 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1

==== CHANNEL f1 =====
SF01 100.6278588 MHz
NUC1 13C
P1 10.00 usec
PLW1 64.00000000 W

==== CHANNEL f2 =====
SF02 400.1516006 MHz
NUC2 1H
CPDPRG2 waltz16
PCPD2 90.00 usec
PLW2 29.00000000 W
PLWI2 0.35802001 W
PLWI3 0.289999999 W

F2 - Processing parameters
SI 32768
SF 100.6177980 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40



Approximate three-dimensional chemical space of five cyclic peptides. Each data point in the graph represents a group of peptides with the core scaffold indicated in the figure legend. The chemical space was constructed using Tanimoto similarity based on MACCS key fingerprints. The similarity matrix was then subjected to principal component analysis, and the first three principal components, which explained 96.8% of the total variance of the sample, were plotted in the figure. A similar approach has been employed to compare the chemical space of other data sets (Reference 43). It is clear from the figure that the thiazole containing cyclic peptides (the green spot near the 'floor' of the graph) occupy a significantly different region in chemical space when compared to the other cyclic peptides illustrated.