

Supporting Information

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Identification of Selective Inhibitors of the Potassium Channel Kv1.1–1.2₍₃₎ by High-Throughput Virtual Screening and Automated Patch Clamp

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cmdc_201100600_sm_miscellaneous_information.pdf

Table S1: Original ranks of the 14 hits according to the implementations A and B and the three used consensus scoring methods, rank2max, rank2number and rank2rank.

| ID | Implementation A | | | Implementation B | | | IC50 |
|----|------------------|-------------|-----------|------------------|-------------|-----------|------|
| | rank2max | rank2number | rank2rank | rank2max | rank2number | rank2rank | |
| 1 | 94 | 216 | 55 | n.e. | n.e. | n.e. | 0.71 |
| 2 | 121 | 373 | 225 | n.e. | n.e. | n.e. | 0.79 |
| 3 | 86 | 575 | 181 | n.e. | n.e. | n.e. | 1.41 |
| 4 | 170 | 228 | 208 | n.e. | n.e. | n.e. | 1.62 |
| 5 | 72 | 455 | 132 | n.e. | n.e. | n.e. | 2.98 |
| 6 | 91 | 410 | 91 | n.e. | n.e. | n.e. | 4.07 |
| 7 | 80 | 583 | 152 | 8 | 35 | 10 | 1.53 |
| 8 | 2399 | 2084 | 1137 | 68 | 184 | 115 | 0.58 |
| 9 | 418 | 1086 | 333 | 9 | 70 | 23 | 0.93 |
| 10 | 323 | 471 | 315 | 7 | 23 | 8 | 1.66 |
| 11 | 1204 | 782 | 352 | 133 | 88 | 73 | 2.71 |
| 12 | 3563 | 1805 | 1401 | 137 | 112 | 53 | 3.7 |
| 13 | 267 | 740 | 444 | 13 | 51 | 30 | 3.77 |
| 14 | 303 | 754 | 354 | 112 | 78 | 100 | 5.94 |

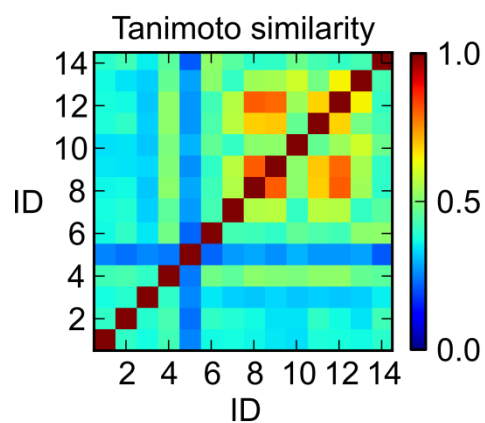


Figure S1. Tanimoto-similarity of the 14 active compounds.

Table S2: BEDROC and AROC values according to scores and subscores of Vina, Glide, eHiTS and FlexX.

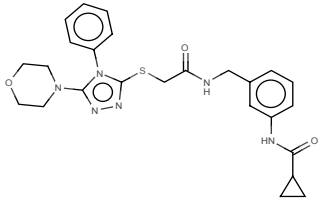
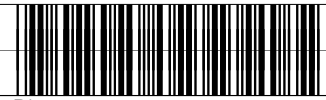
| Score/Sub-Score | BEDROC | AROC |
|-------------------------|--------|--------|
| Autodock-Vina | 0.5191 | 0.706 |
| FlexX_Ambig-Score | 0.2356 | 0.5589 |
| FlexX_AnzMatch | 0.1066 | 0.4086 |
| FlexX_AvgVolume | 0.1325 | 0.5001 |
| FlexX_Clash-Score | 0.0422 | 0.392 |
| FlexX_Lipo-Score | 0.5898 | 0.7029 |
| FlexX_Match-Score | 0.0232 | 0.3718 |
| FlexX_MaxVolume | 0.0904 | 0.4485 |
| FlexX_Rot-Score | 0.1874 | 0.4307 |
| FlexX_Total-Score | 0.1094 | 0.4387 |
| ChemScore_Clash-Score | 0.1049 | 0.4641 |
| ChemScore_FragNo | 0.239 | 0.3545 |
| ChemScore_Lipo-Score | 0.5485 | 0.7312 |
| ChemScore_Match-Score | 0.0106 | 0.327 |
| ChemScore_MaxVolume | 0.1068 | 0.4917 |
| ChemScore_Rot-Score | 0.2193 | 0.4657 |
| ChemScore_Total-Score | 0.3361 | 0.6317 |
| Glide_XP-Electro | 0.0256 | 0.3793 |
| Glide_XP-HBond | 0.0215 | 0.3804 |
| Glide_XP-LipophilicEvdW | 0.6058 | 0.7254 |
| Glide_XP-Penalties | 0.1741 | 0.4052 |
| Glide_XP-PhobicPenal | 0.2063 | 0.5101 |
| Glide_XP-RotPenal | 0.0696 | 0.5022 |
| Glide_XP-Sitemap | 0.3578 | 0.6 |
| Glide_ecoul | 0.0259 | 0.3851 |
| Glide_einternal | 0.1101 | 0.392 |
| Glide_emodel | 0.5611 | 0.7073 |
| Glide_energy | 0.5393 | 0.6945 |
| Glide_evdw | 0.67 | 0.7406 |
| Glide_gscore | 0.3146 | 0.5475 |
| eHiTS_Energy | 0.3355 | 0.6136 |
| eHiTS_Score | 0.1648 | 0.5041 |
| eHiTS_Term-Coulomb | 0.1632 | 0.5416 |
| eHiTS_Term-H_bond | 0.0894 | 0.4321 |
| eHiTS_Term-Lcover | 0.1312 | 0.4798 |
| eHiTS_Term-Lipophil | 0.124 | 0.4542 |
| eHiTS_Term-LlogD | 0.0861 | 0.3868 |
| eHiTS_Term-Rcharge | 0.0529 | 0.3715 |
| eHiTS_Term-Rcover | 0.2297 | 0.4745 |
| eHiTS_Term-RlogD | 0.2451 | 0.5364 |
| eHiTS_Term-Rshape | 0.298 | 0.5632 |
| eHiTS_Term-depth | 0.4401 | 0.6932 |
| eHiTS_Term-entropy | 0.0513 | 0.3396 |
| eHiTS_Term-family | 0.4456 | 0.7025 |
| eHiTS_Term-other | 0.2119 | 0.5413 |
| eHiTS_Term-pi_stack | 0.2414 | 0.533 |
| eHiTS_Term-solvent | 0.2521 | 0.6055 |
| eHiTS_Term-steric | 0.3027 | 0.5495 |
| eHiTS_Term-strain | 0.5824 | 0.7351 |

| Table S3: Inhibitors of Kv1.1 and Kv1.2. Sources: Drug Bank, Tocris Bioscience. NA stands for Data Not Available and "-" no indication of particular target | | | | | |
|--|-------------|-----------|--------------------|--------------------|--|
| Name/INN | CAS | Pubmed ID | Kv1.1 IC50 (µM) | Kv1.2 IC50 (µM) | Other targets/ IC50 (µM) |
| Nifedipine | 21829-25-4 | 7517498 | NA | NA | NA |
| Amitriptyline | 50-48-6 | 17456683 | 22 | - | Kv7.2/7.3 10 |
| 4-Aminopyridine Fampridine | 504-24-5 | 19413590 | 170 | 230 | Kv1.4, Kv4.2 |
| Nerispidine | 119229-65-1 | 19413590 | 3.6 | 3.7 | NavX 11.9 |
| AM 92016 hydrochloride | 178894-81-0 | 15967421 | NA | NA | NA |
| KN-93 | 139298-40-1 | 16368898 | - | 1 | Kv1.4, Kv1.5, Kv2.1, Kv3.2, Kv4.2 hERG |

Spectral Data

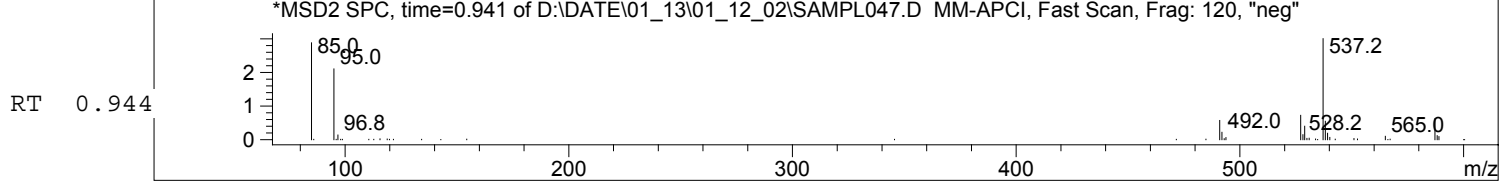
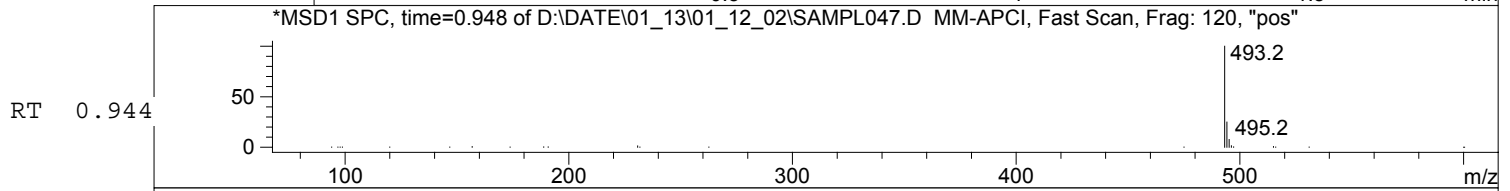
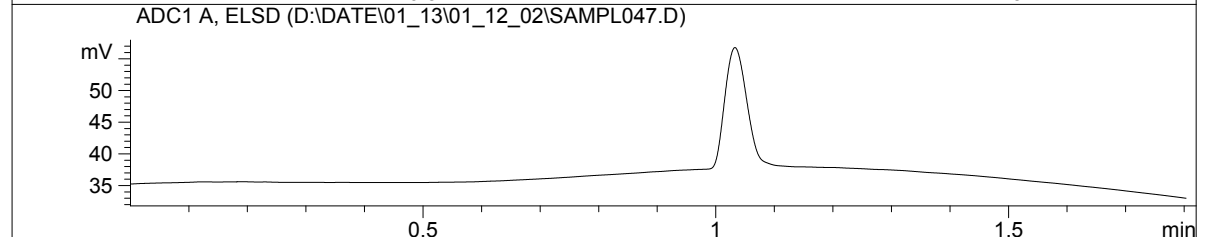
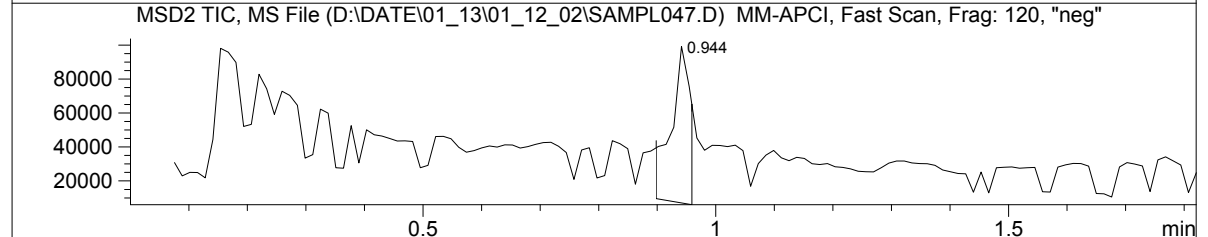
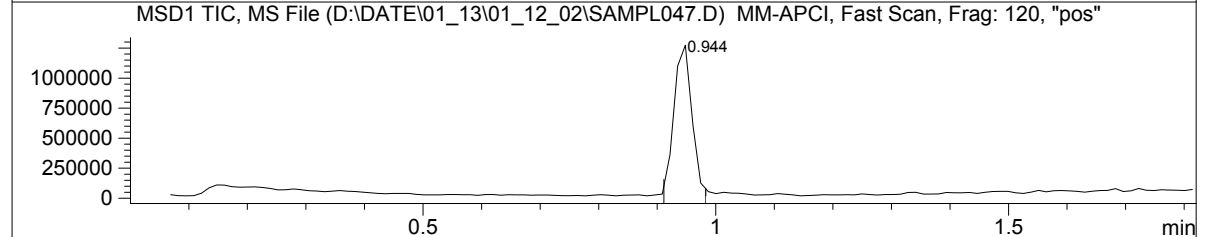
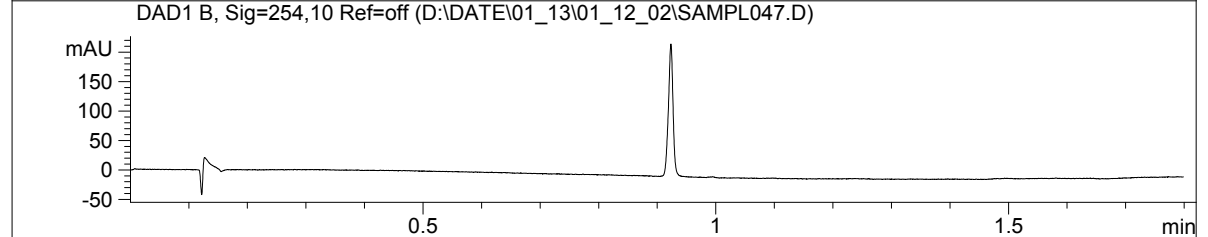
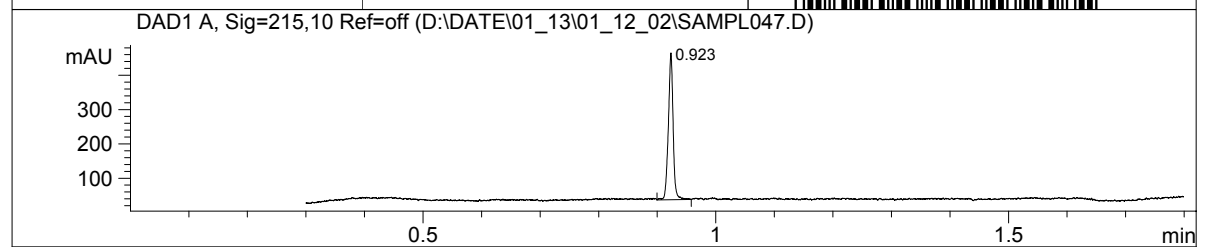
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Ret_Time: 0.923 min

4532116



Mol Wt 492.593
Exact Mass 492.22

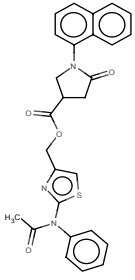
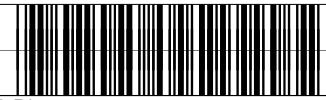
| # | Time | Area% |
|---|-------|--------|
| 1 | 0.923 | 100.00 |



Compound ID: 1

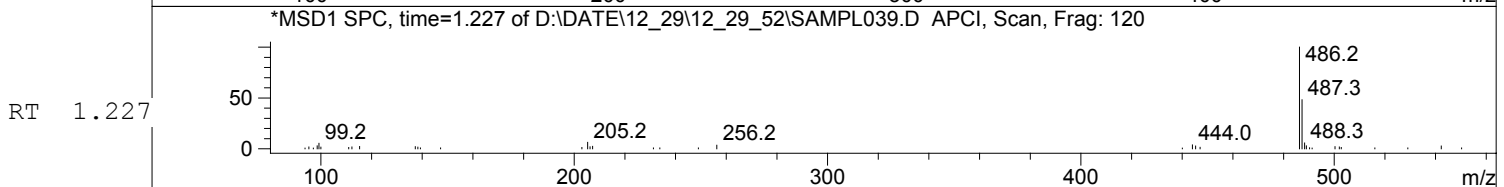
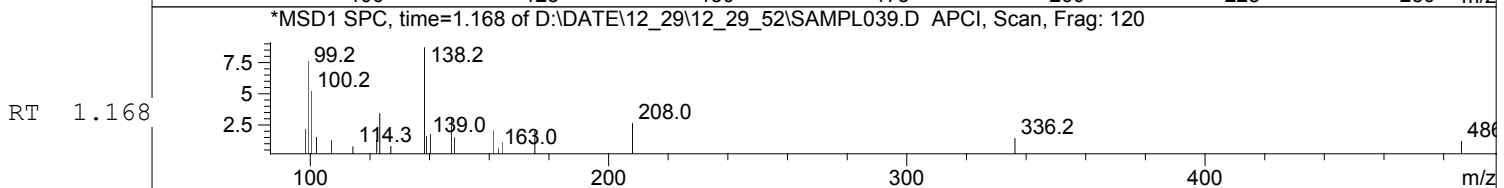
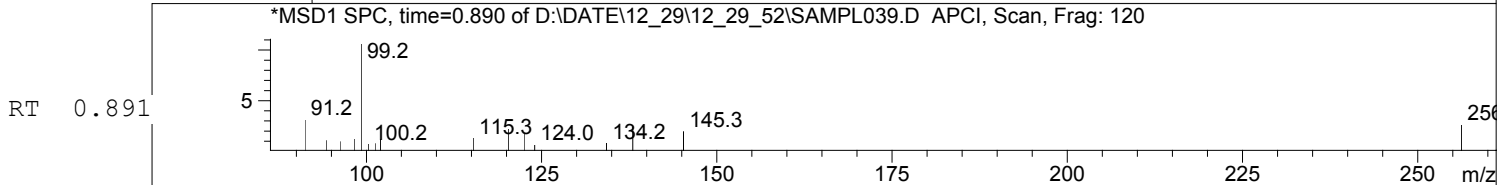
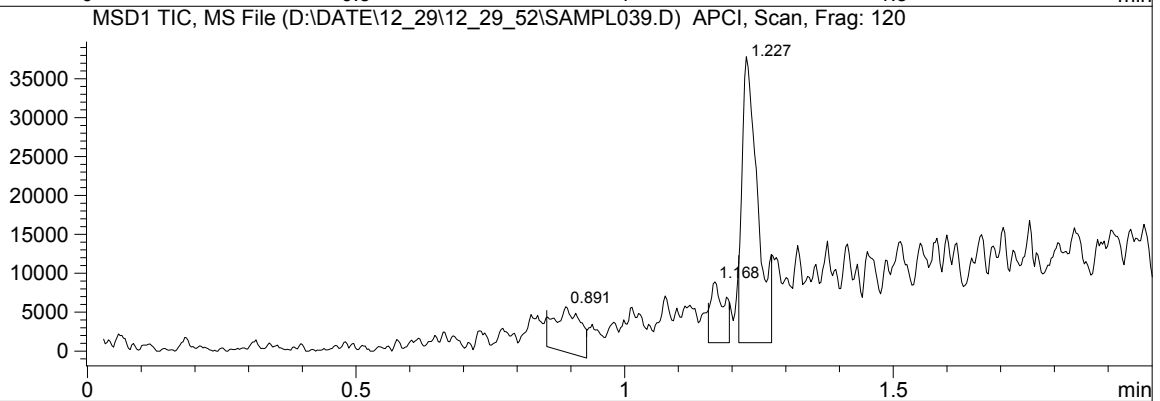
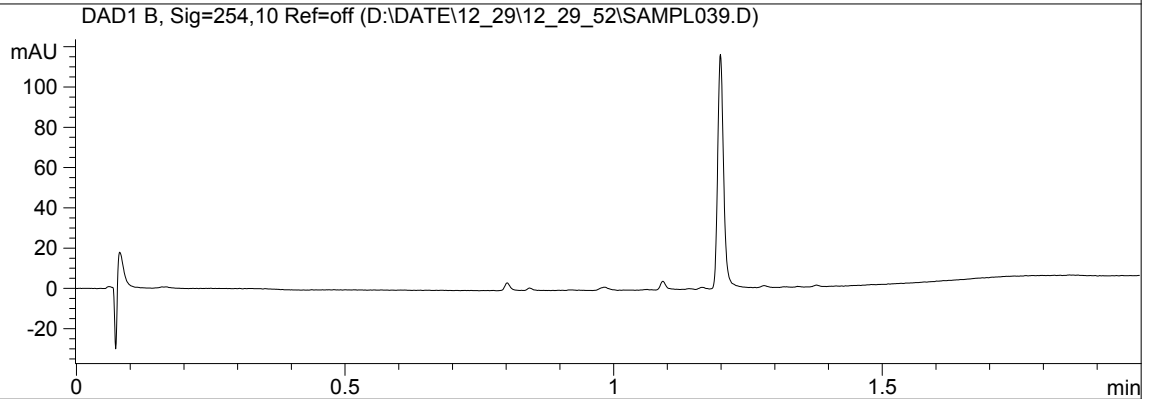
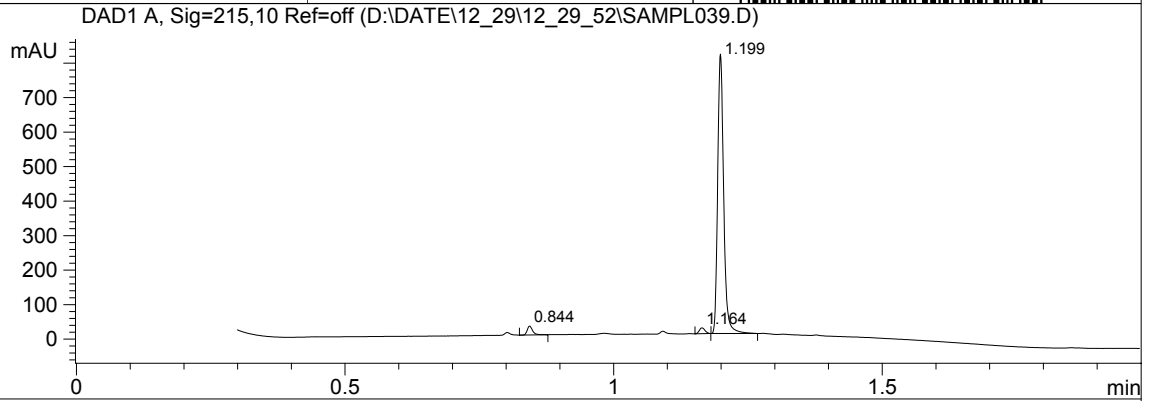
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Ret_Time: 1.199 min

4532085



Mol Wt 485.554
Exact Mass 485.16

| # | Time | Area% |
|---|-------|-------|
| 1 | 0.844 | 2.73 |
| 2 | 1.164 | 1.88 |
| 3 | 1.199 | 95.39 |

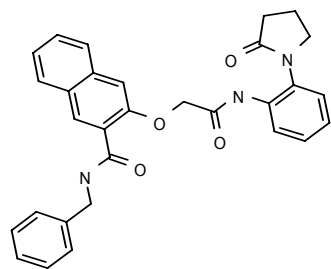
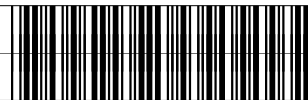


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MaxPeak: 94.09%
Ret_Time: 0.740 min

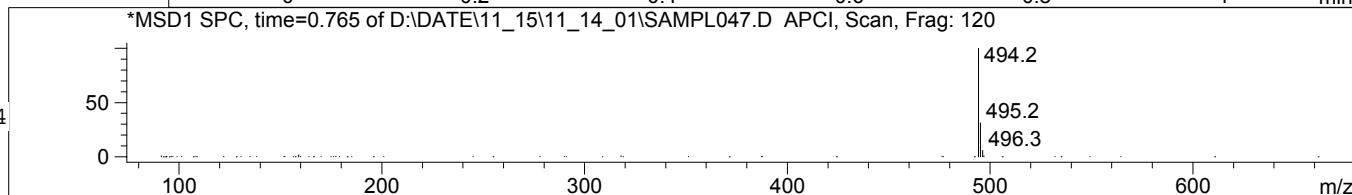
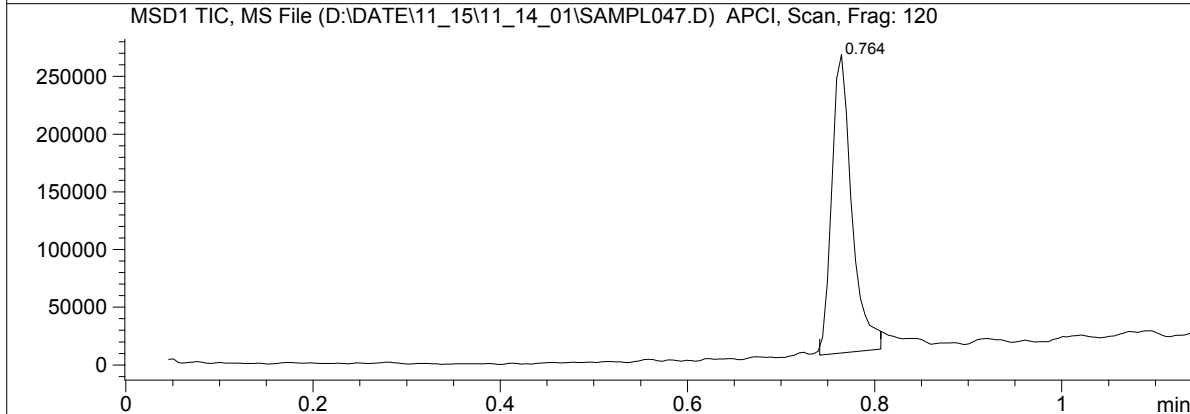
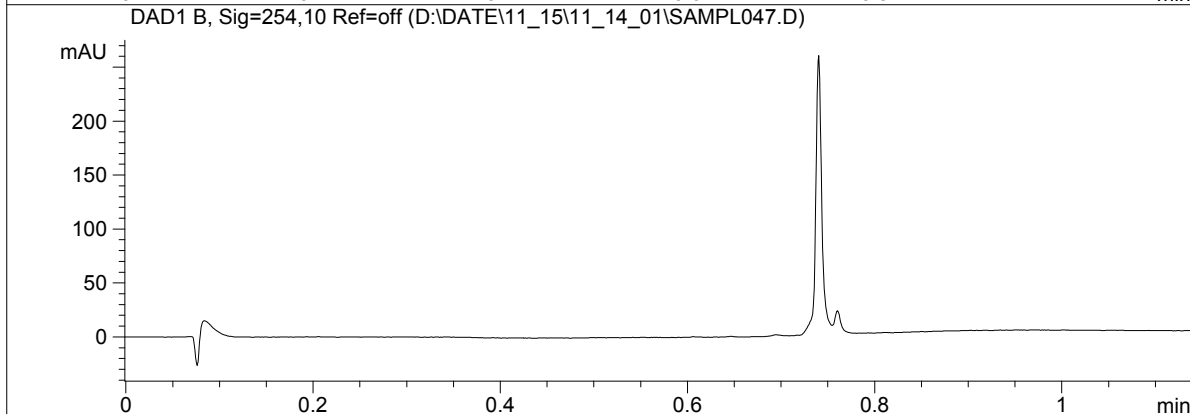
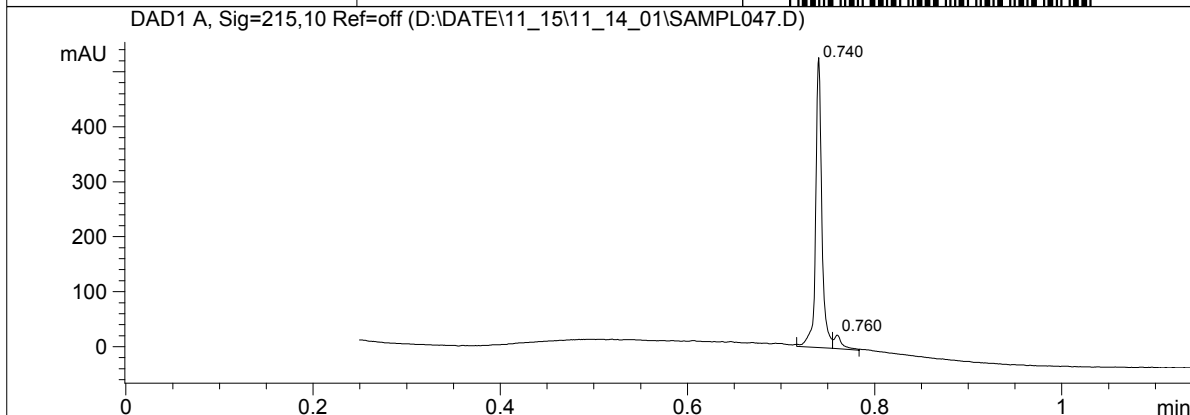
2013129

OK



mw = 493.57

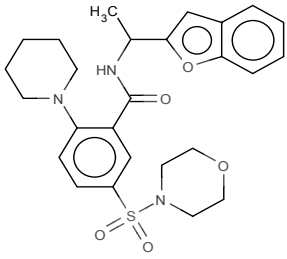
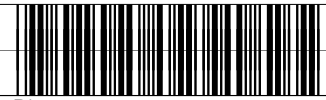
| # | Time | Area% |
|---|-------|-------|
| 1 | 0.740 | 94.09 |
| 2 | 0.760 | 5.91 |



Compound ID: 3

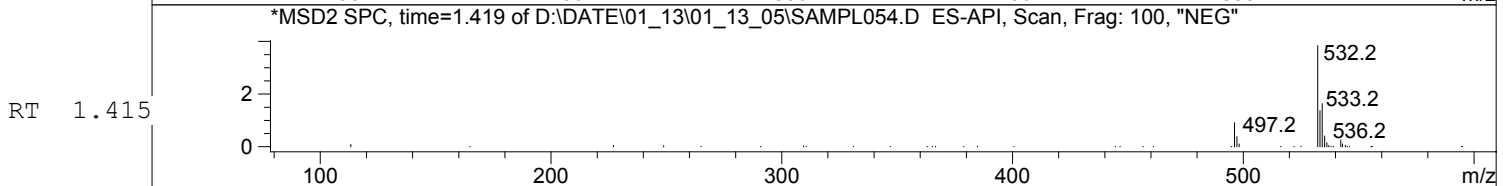
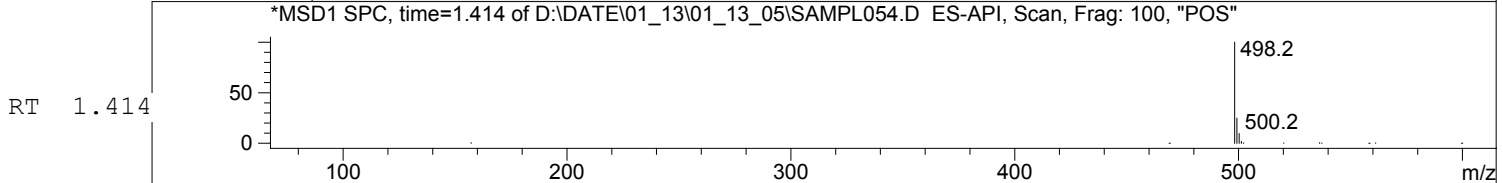
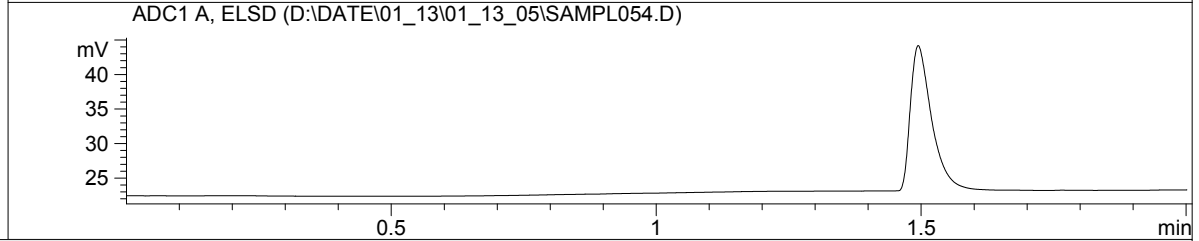
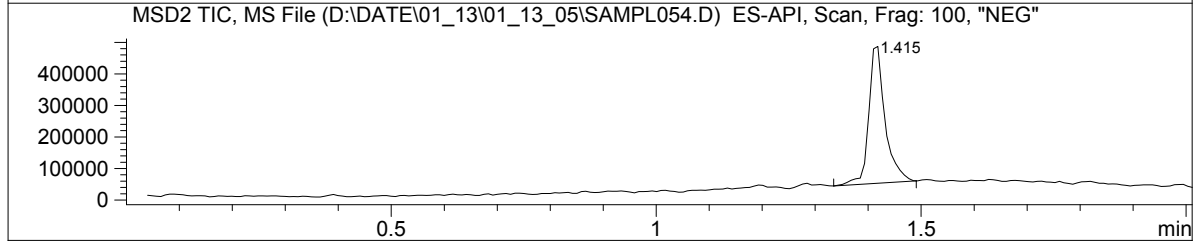
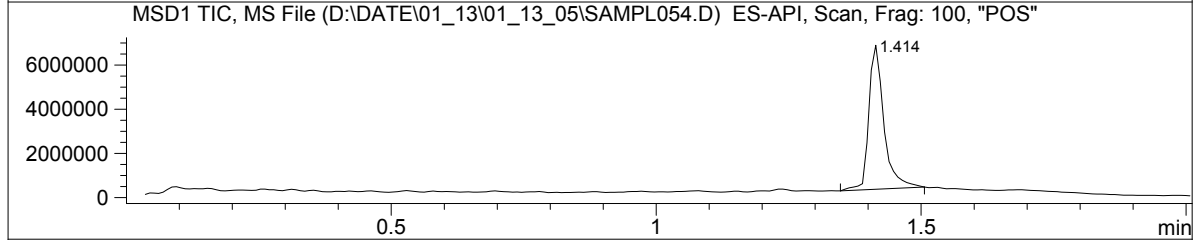
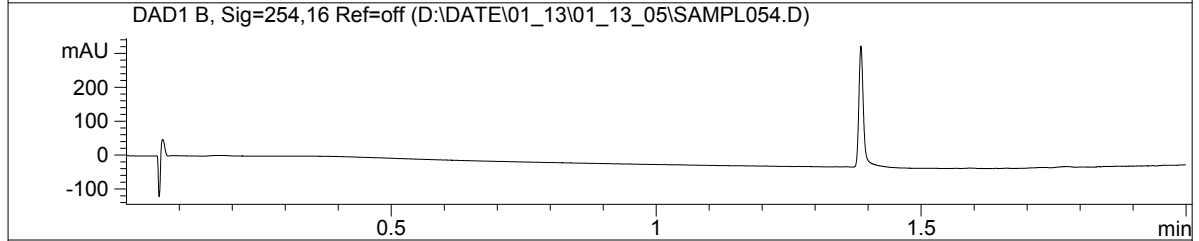
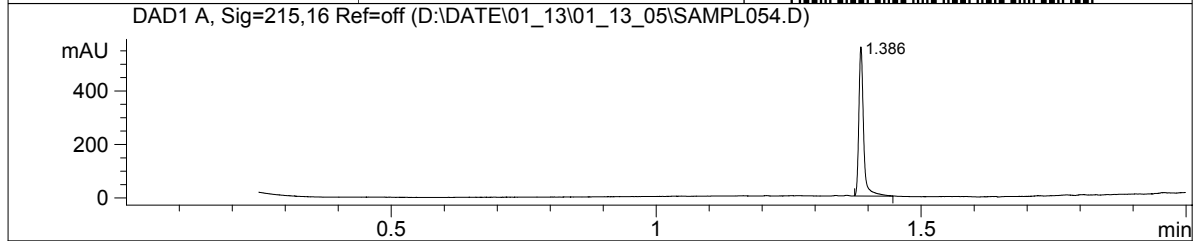
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Ret_Time: 1.386 min

4532160



Mol Wt 497.606
Exact Mass 497.23

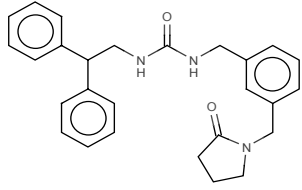
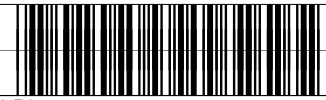
| # | Time | Area% |
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| 1 | 1.386 | 100.00 |



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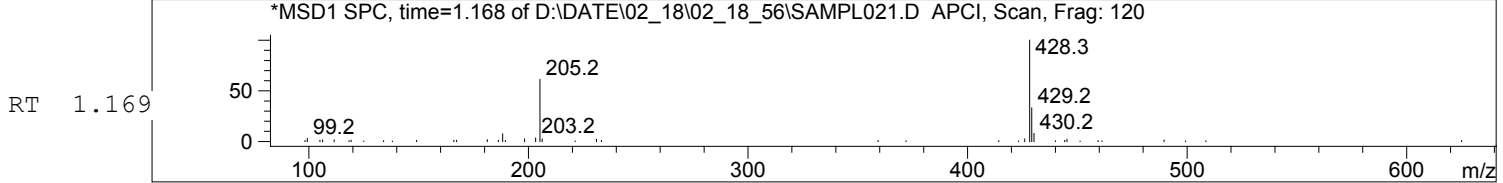
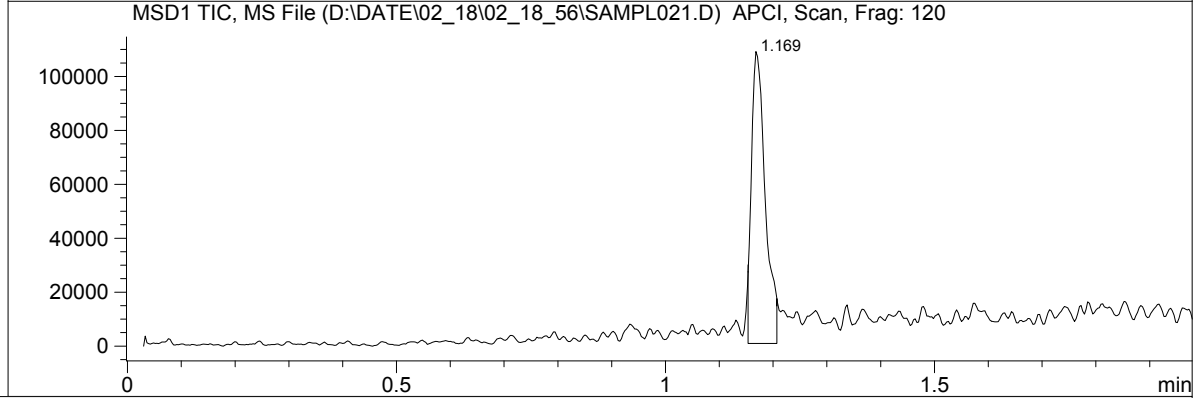
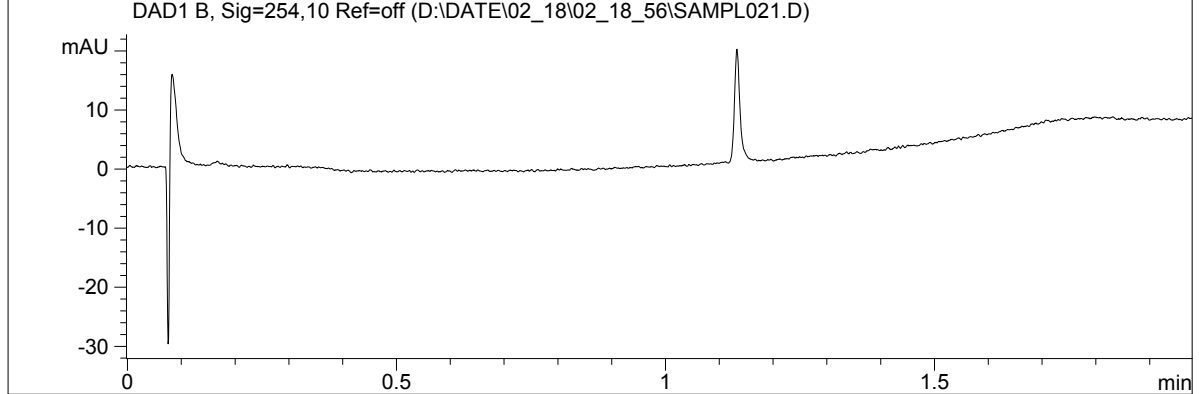
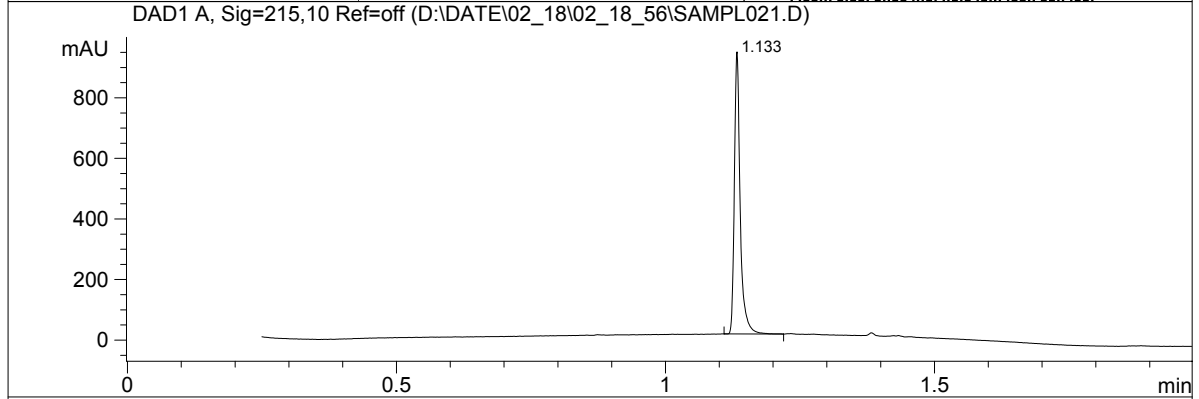
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4531970



Mol Wt 427.538
Exact Mass 427.27

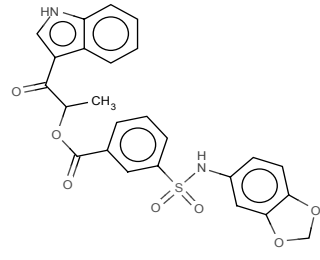
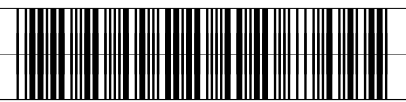
| # | Time | Area% |
|---|-------|--------|
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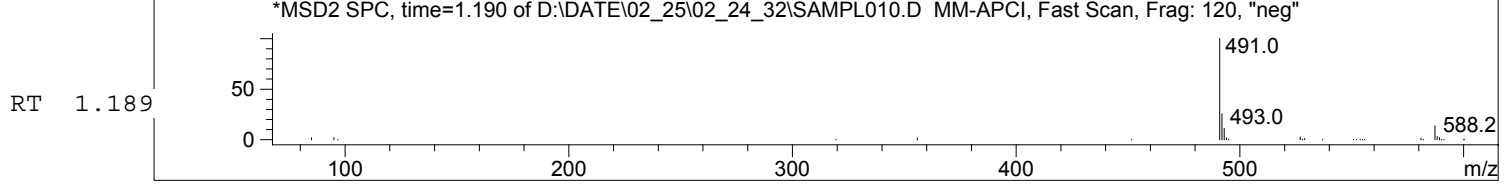
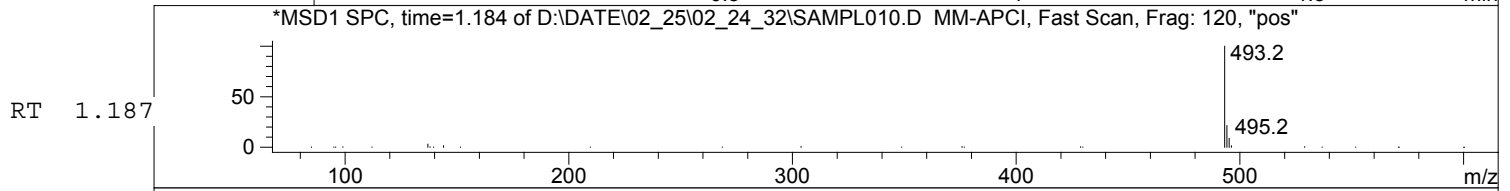
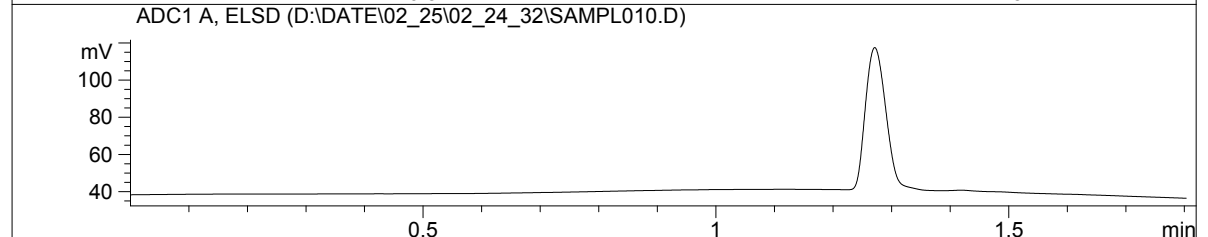
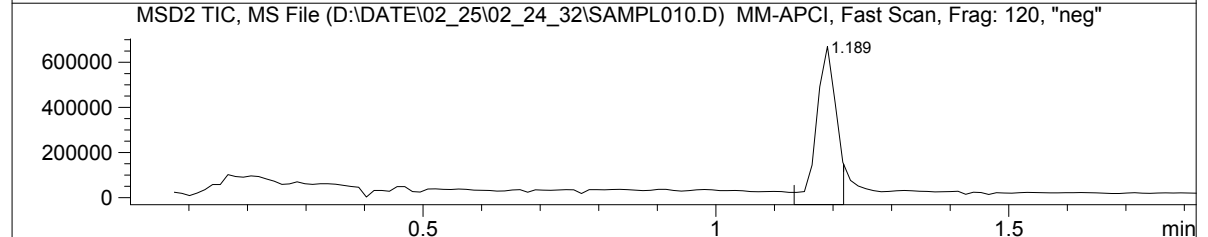
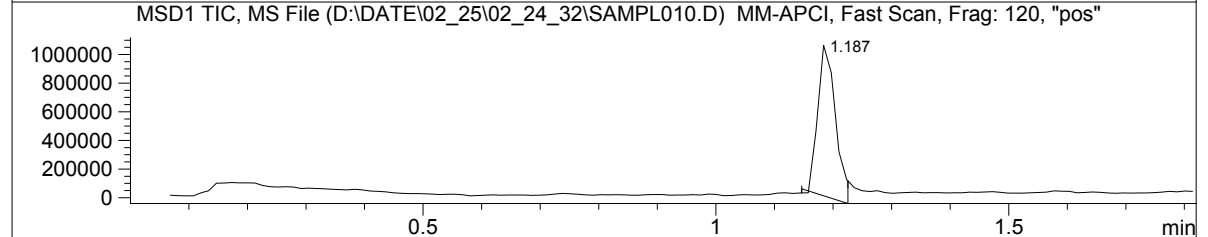
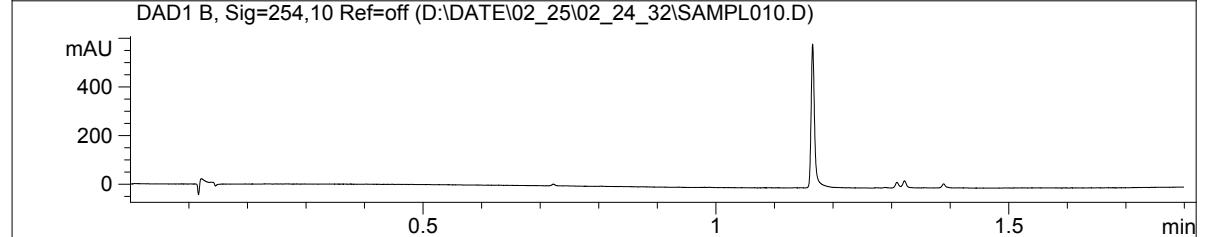
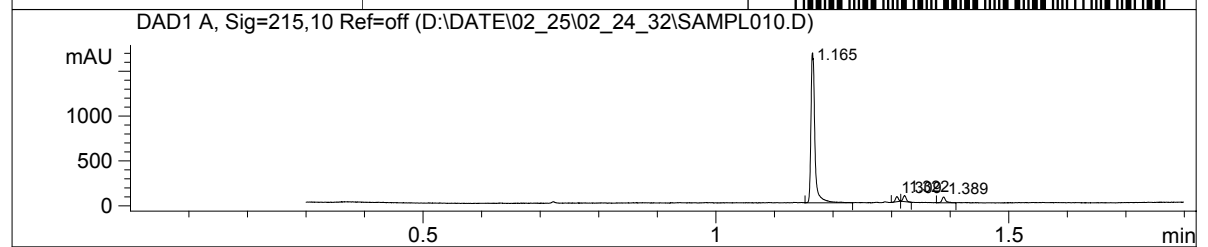
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Ret_Time: 1.165 min

3390363\$2



Mol Wt 492.5
Exact Mass 492.1

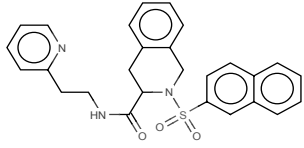
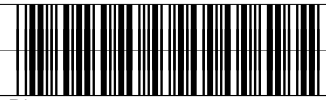
| # | Time | Area% |
|---|-------|-------|
| 1 | 1.165 | 91.31 |
| 2 | 1.309 | 2.31 |
| 3 | 1.322 | 2.91 |
| 4 | 1.389 | 3.48 |



Compound ID: 6

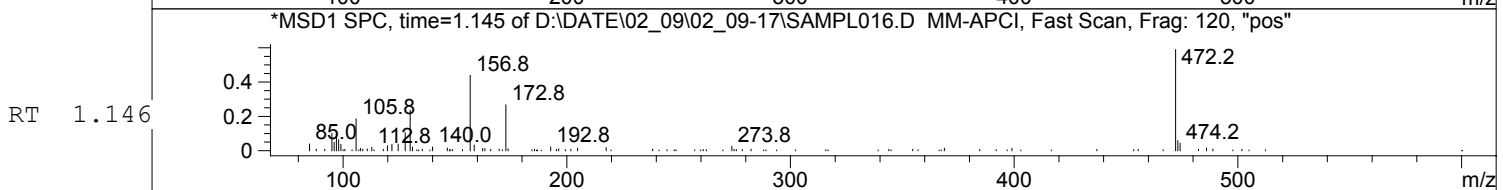
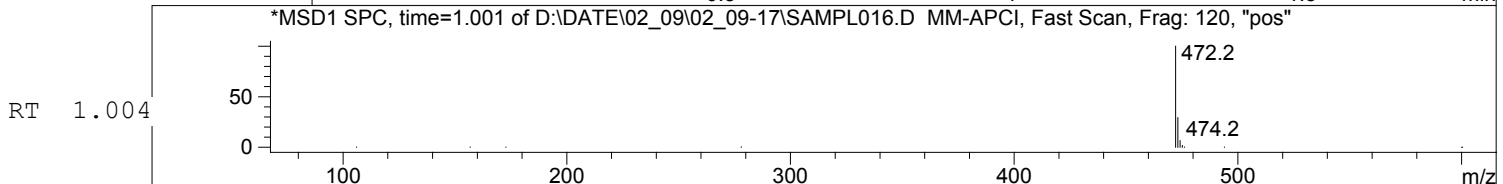
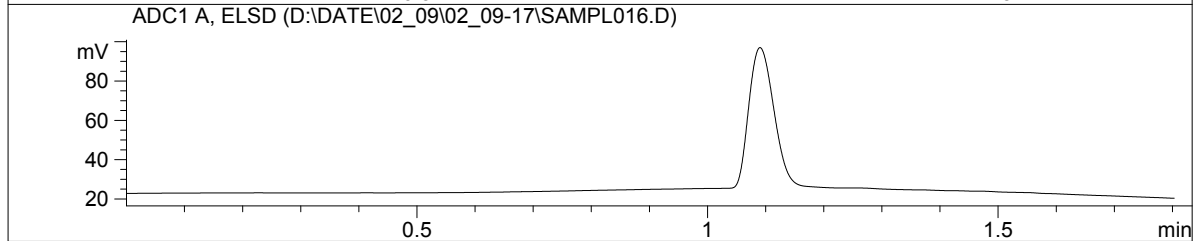
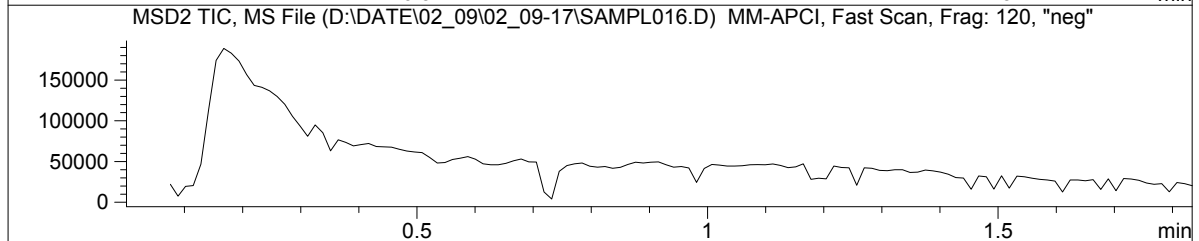
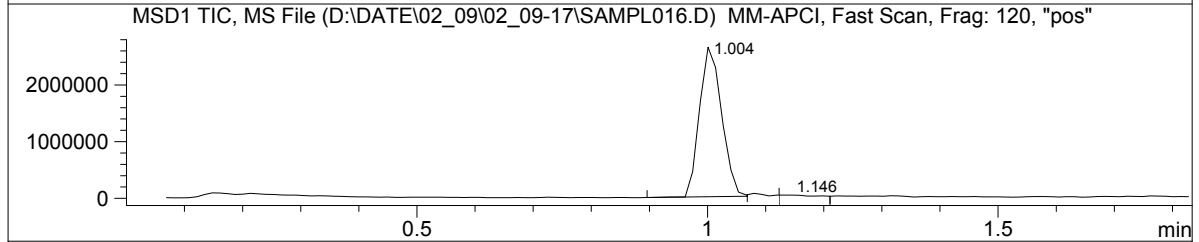
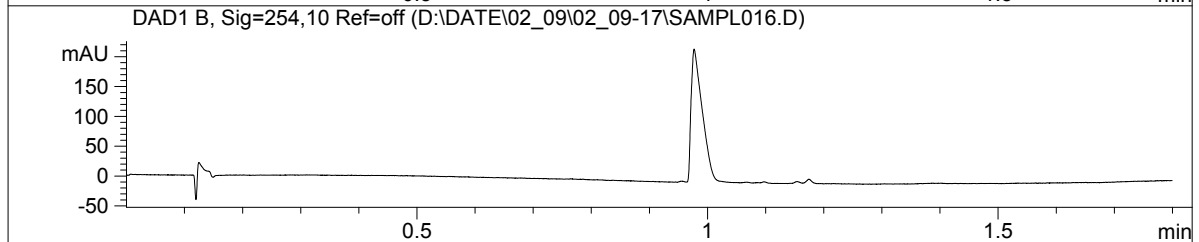
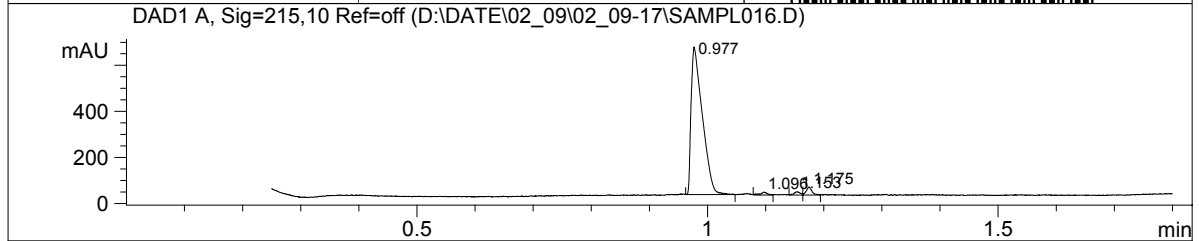
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Ret_Time: 0.977 min

4531990



Mol Wt 471.571
Exact Mass 471.19

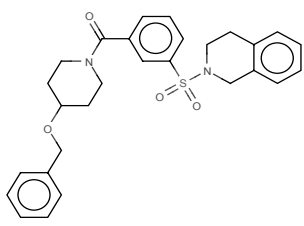
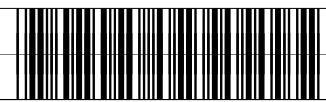
| # | Time | Area% |
|---|-------|-------|
| 1 | 0.977 | 95.13 |
| 2 | 1.096 | 1.15 |
| 3 | 1.153 | 1.15 |
| 4 | 1.175 | 2.56 |



Compound ID: 7

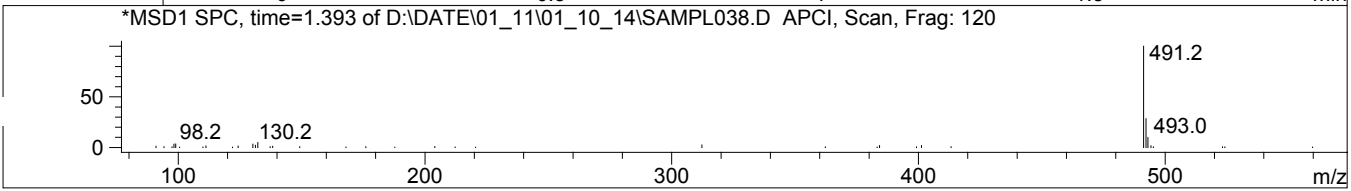
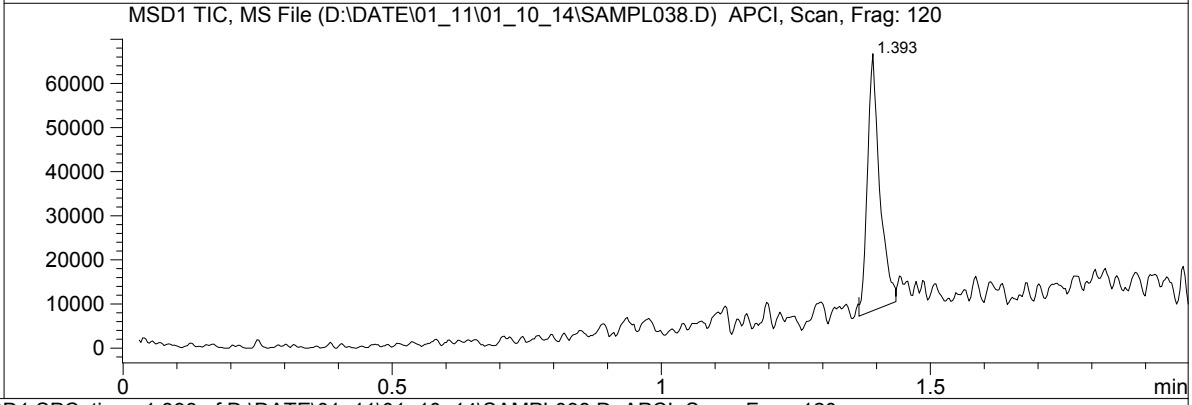
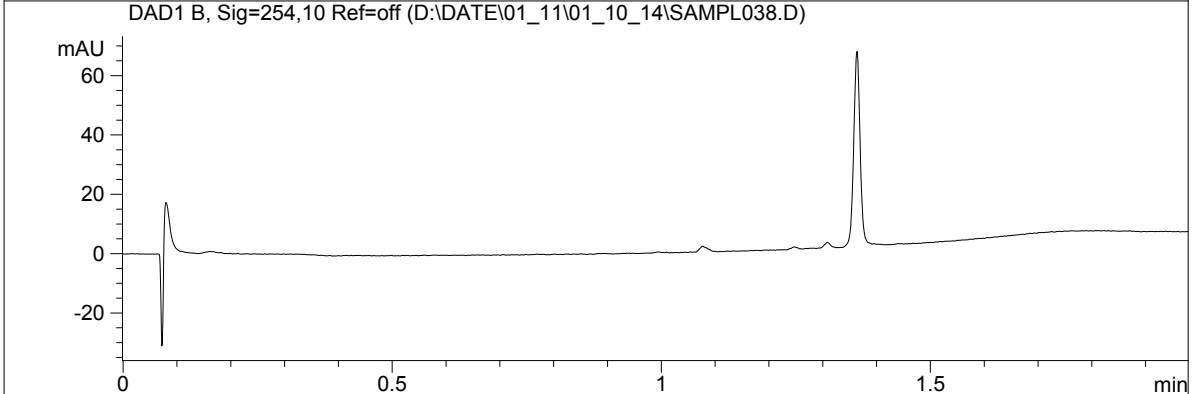
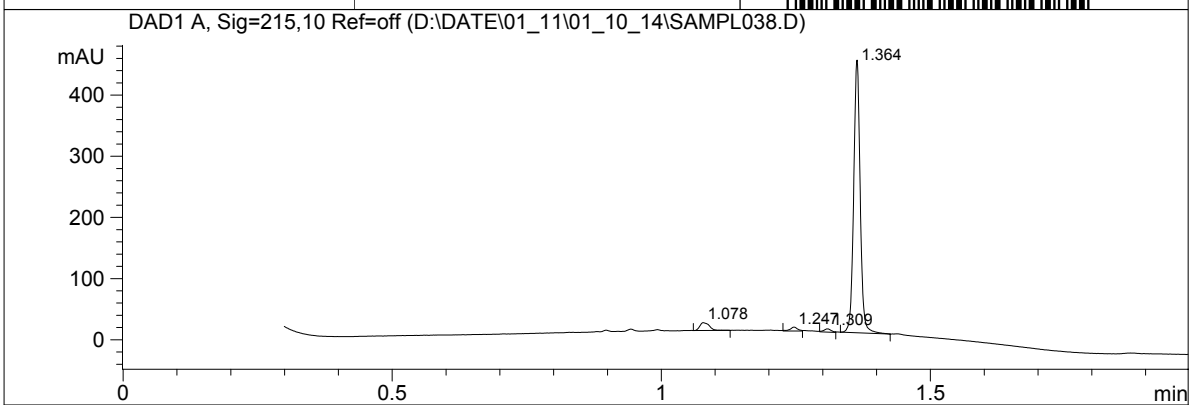
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Ret_Time: 1.364 min

4532129



Mol Wt 490.614
Exact Mass 490.23

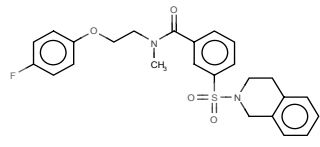
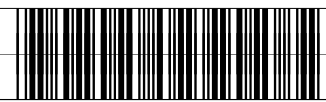
| # | Time | Area% |
|---|-------|-------|
| 1 | 1.078 | 3.92 |
| 2 | 1.247 | 1.58 |
| 3 | 1.309 | 1.28 |
| 4 | 1.364 | 93.22 |



Compound ID: 8

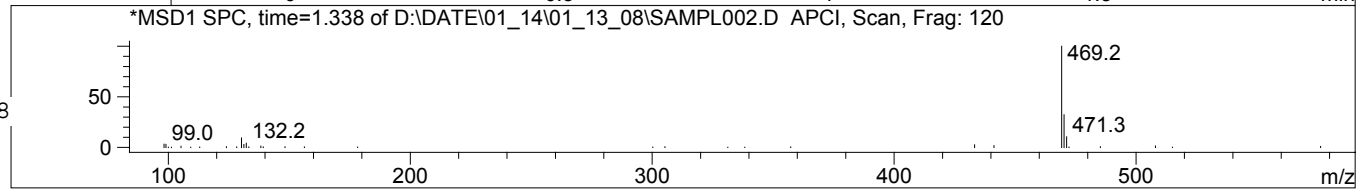
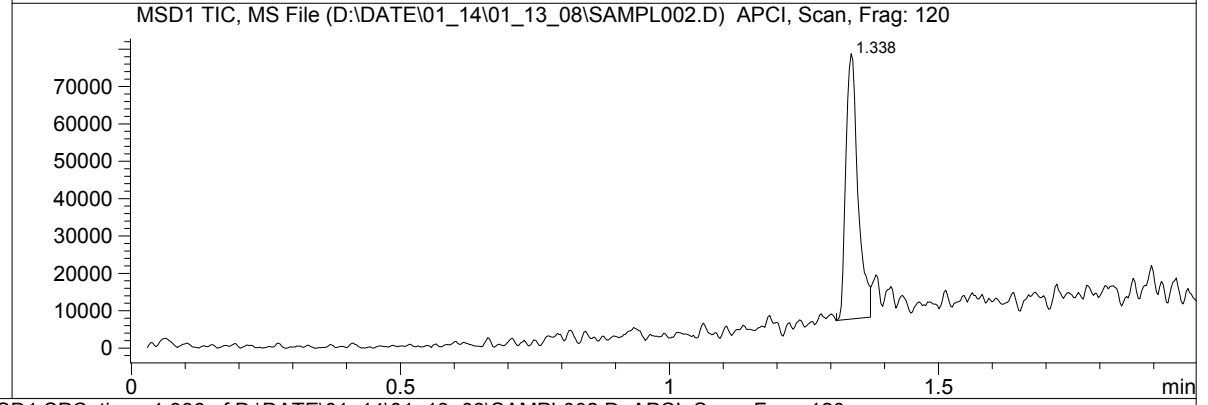
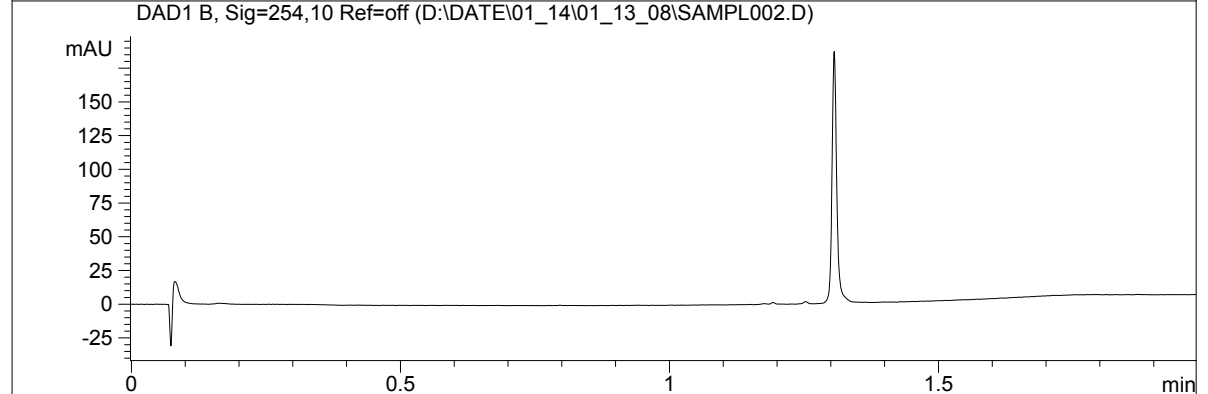
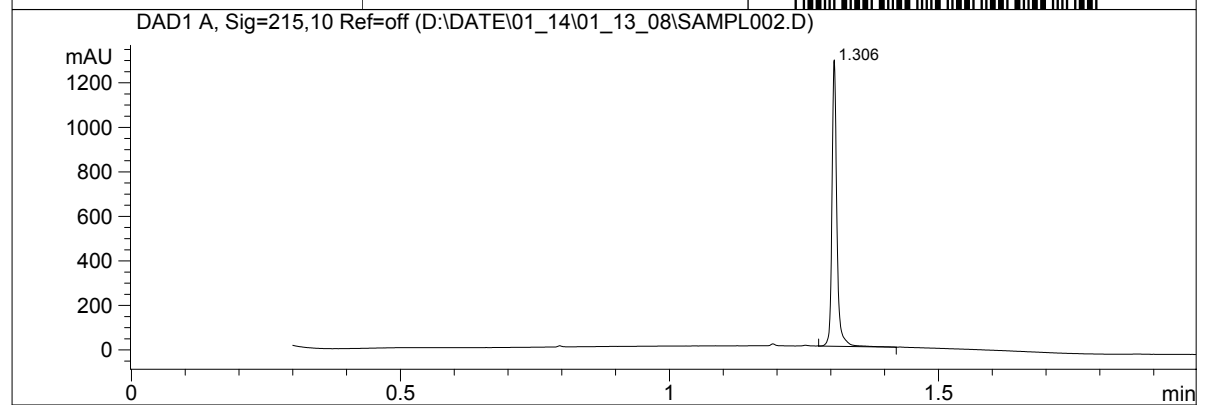
MaxPeak: 100.00%
Ret_Time: 1.306 min

4532153



Mol Wt 468.54
Exact Mass 468.18

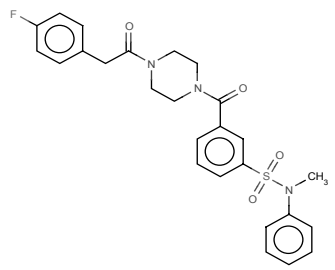
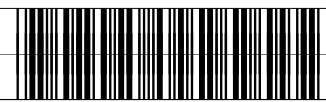
| # | Time | Area% |
|---|-------|--------|
| 1 | 1.306 | 100.00 |



Compound ID: 9

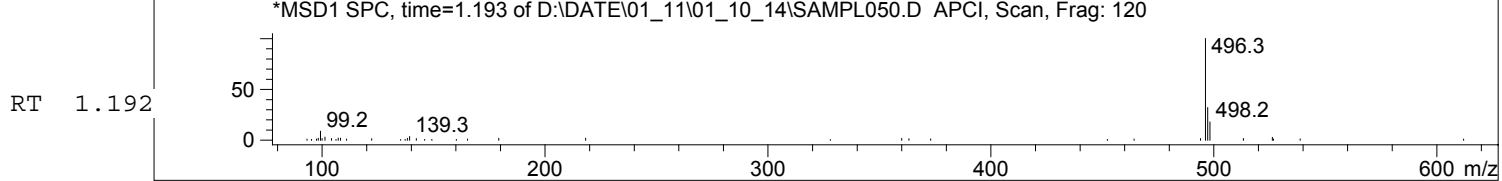
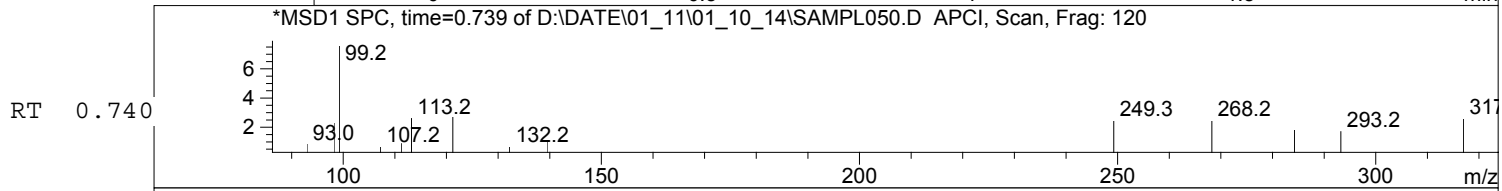
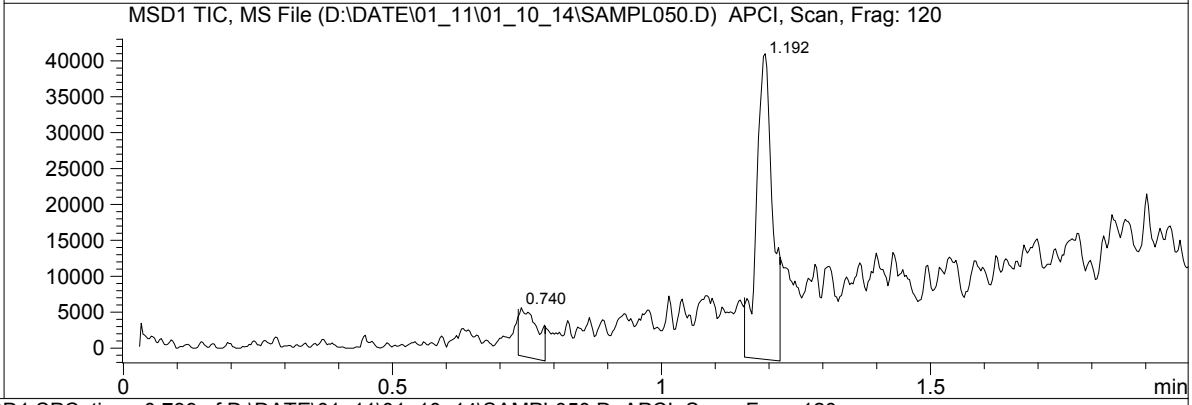
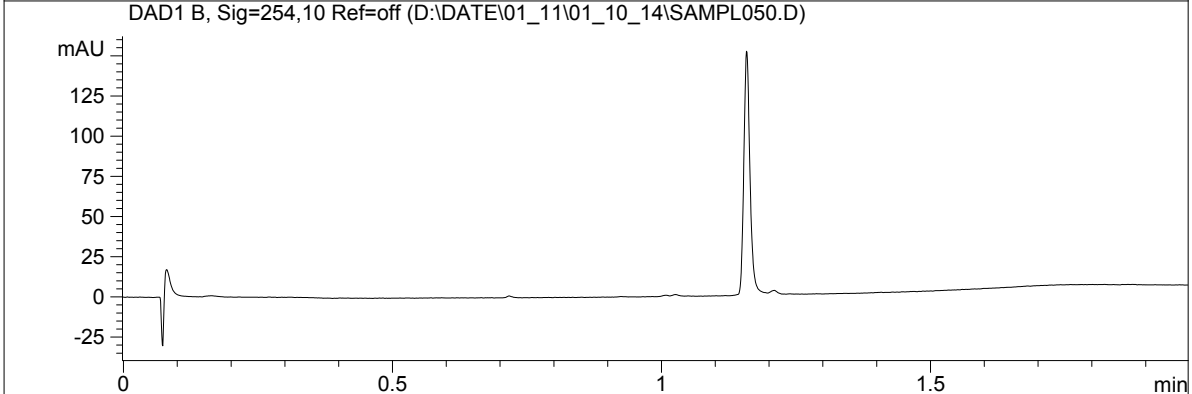
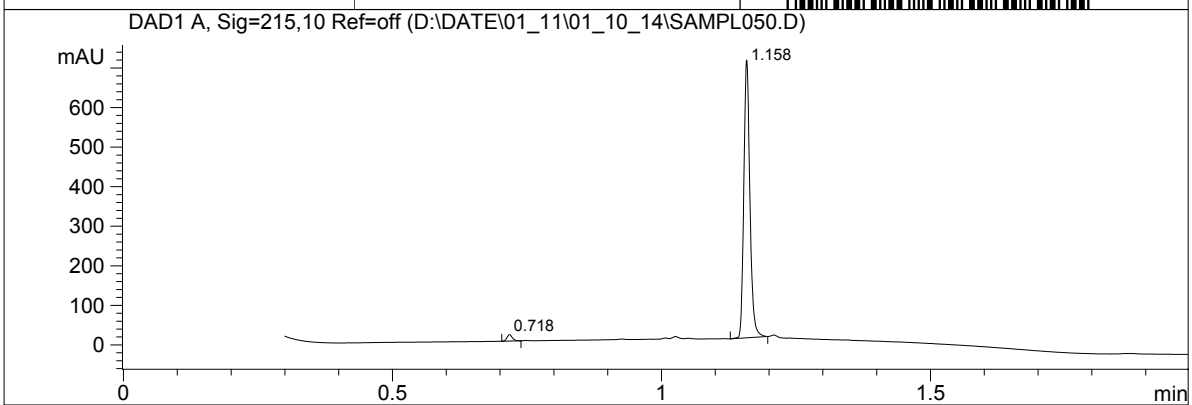
MaxPeak: 97.97%
Ret_Time: 1.158 min

4532004

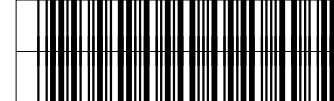


Mol Wt 495.566
Exact Mass 495.19

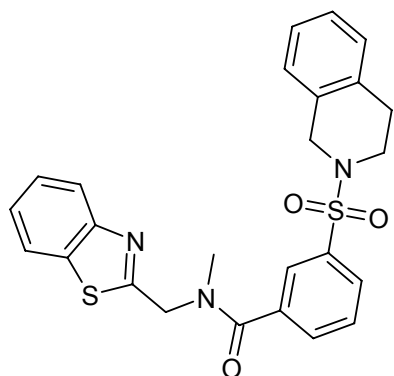
| # | Time | Area% |
|---|-------|-------|
| 1 | 0.718 | 2.03 |
| 2 | 1.158 | 97.97 |



Compound ID: 10

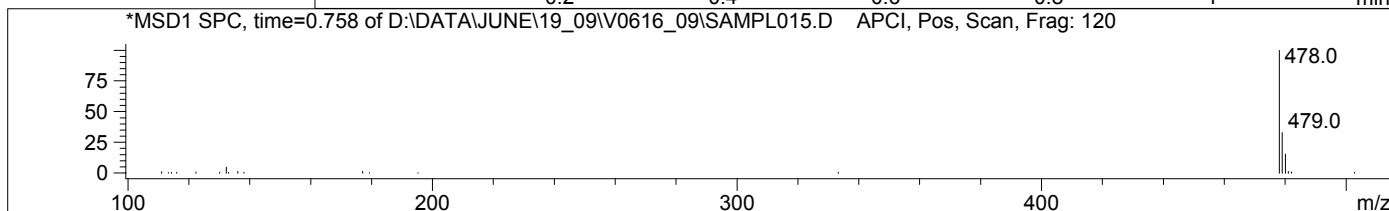
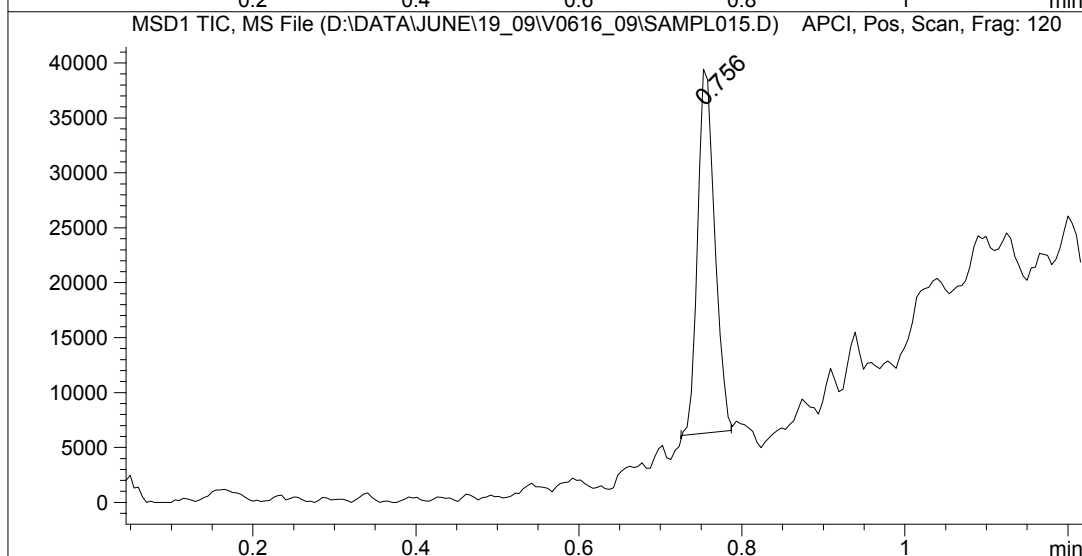
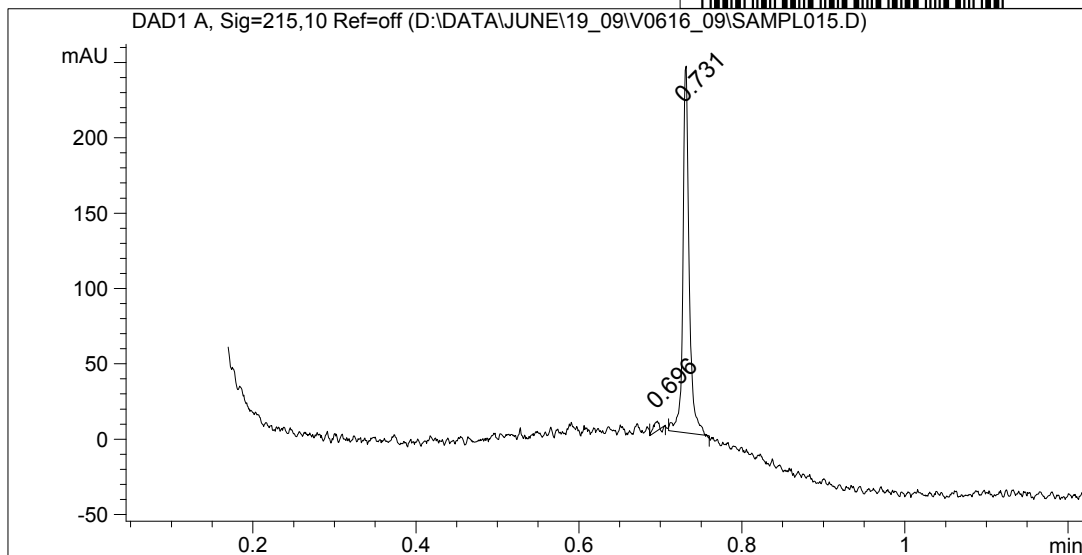


MaxPeak: 97.65%
Ret_Time: 0.731 min



mw = 477,61

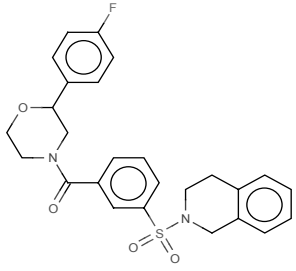
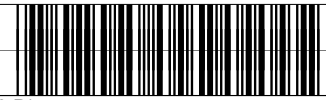
| # | Time | Area% |
|---|-------|-------|
| 1 | 0.696 | 2.35 |
| 2 | 0.731 | 97.65 |



Compound ID: 11

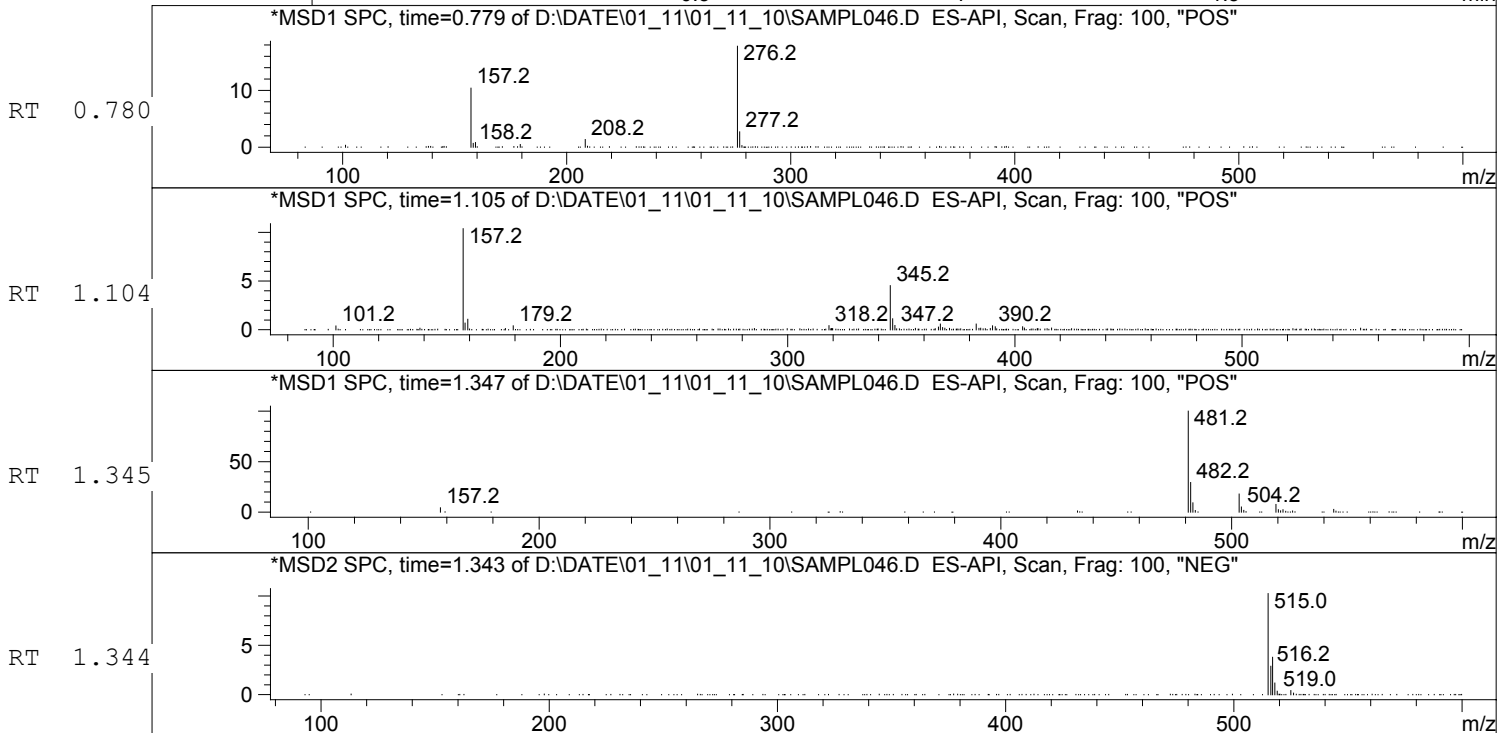
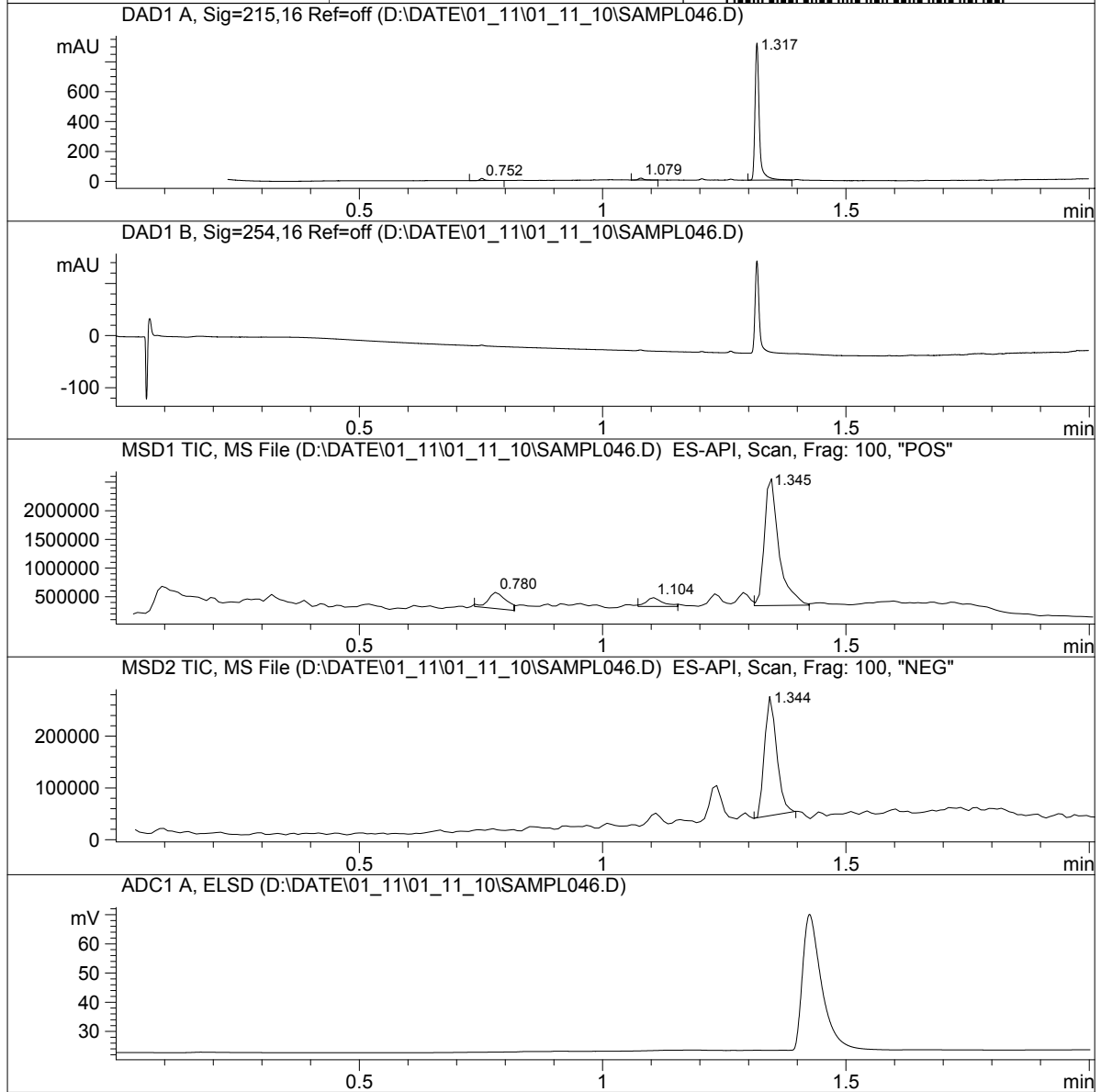
MaxPeak: 96.68%
Ret_Time: 1.317 min

4532022



Mol Wt 480.551
Exact Mass 480.18

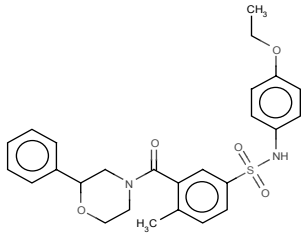
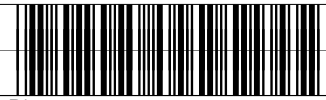
| # | Time | Area% |
|---|-------|-------|
| 1 | 0.752 | 1.71 |
| 2 | 1.079 | 1.61 |
| 3 | 1.317 | 96.68 |



Compound ID: 12

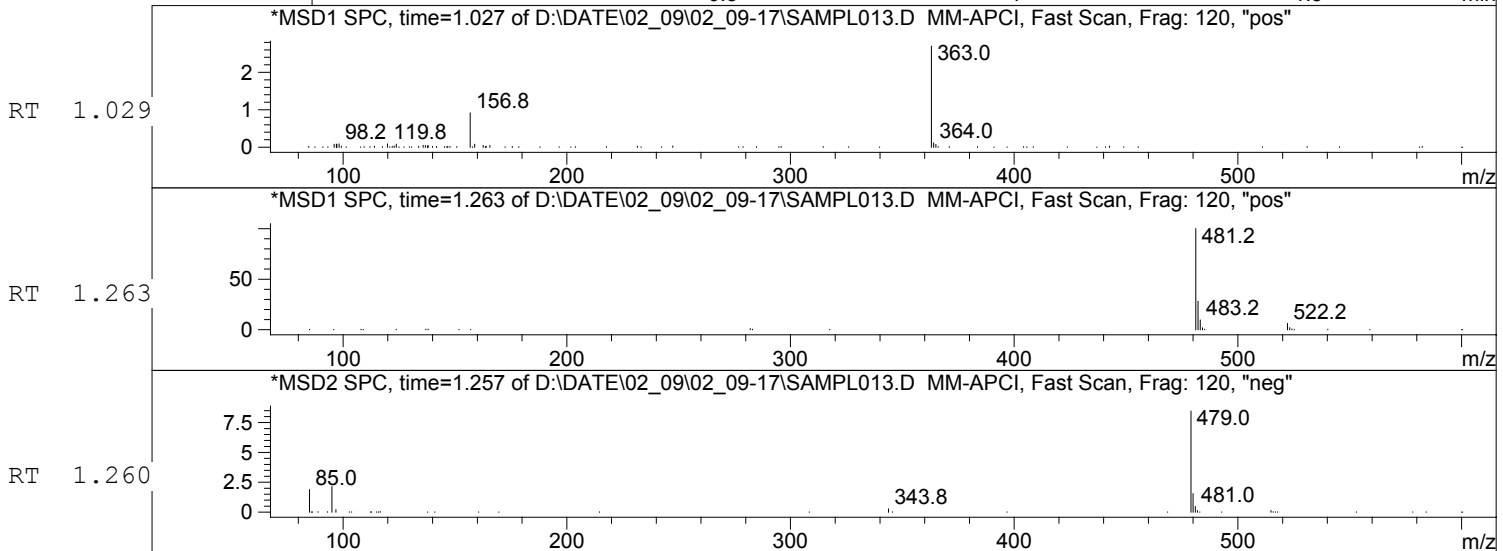
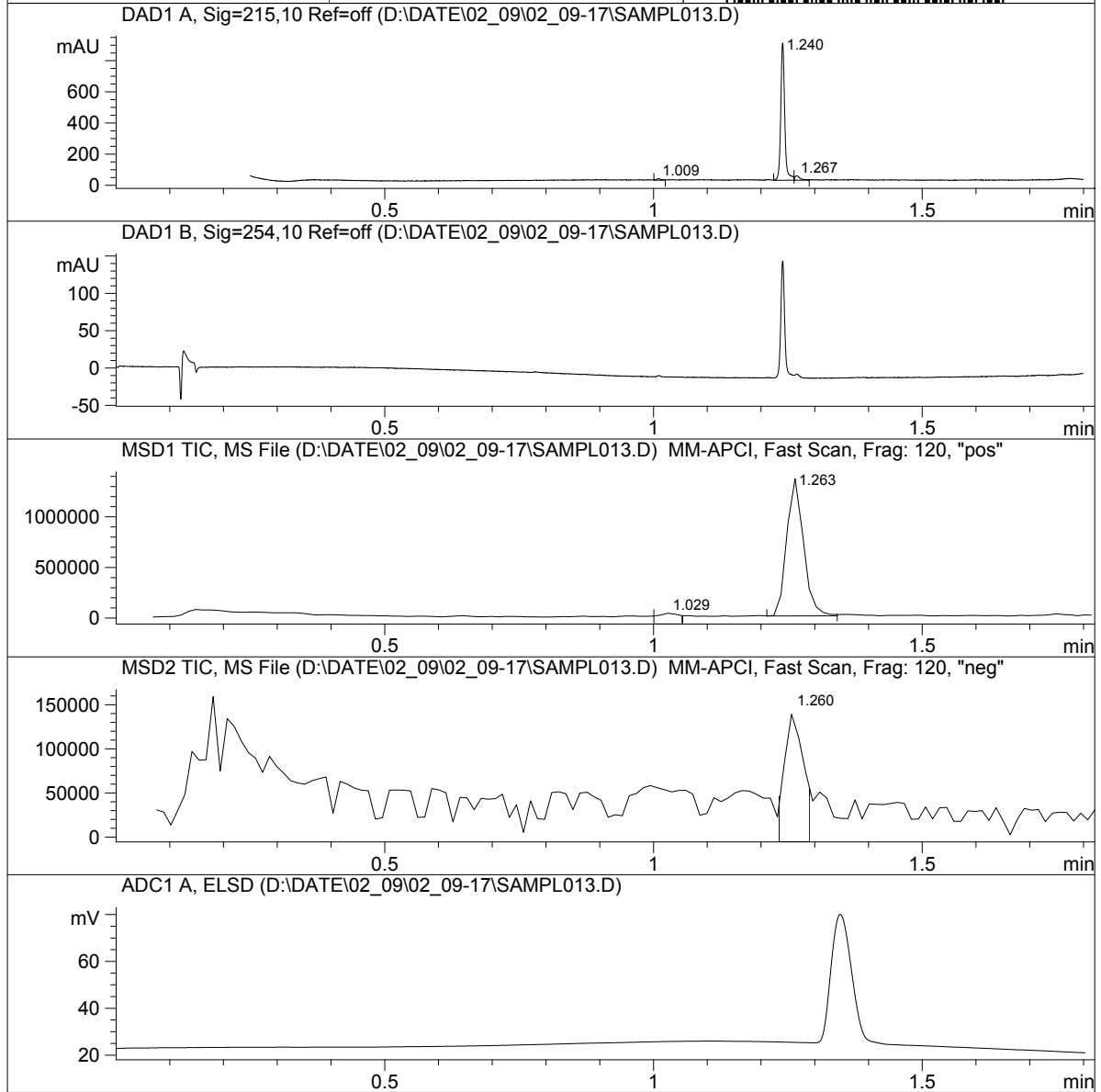
MaxPeak: 94.66%
Ret_Time: 1.240 min

4532001



Mol Wt 480.576
Exact Mass 480.2

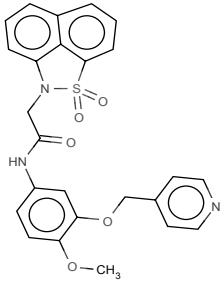
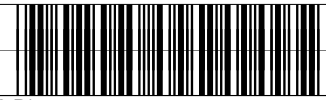
| # | Time | Area% |
|---|-------|-------|
| 1 | 1.009 | 1.14 |
| 2 | 1.240 | 94.66 |
| 3 | 1.267 | 4.19 |



Compound ID: 13

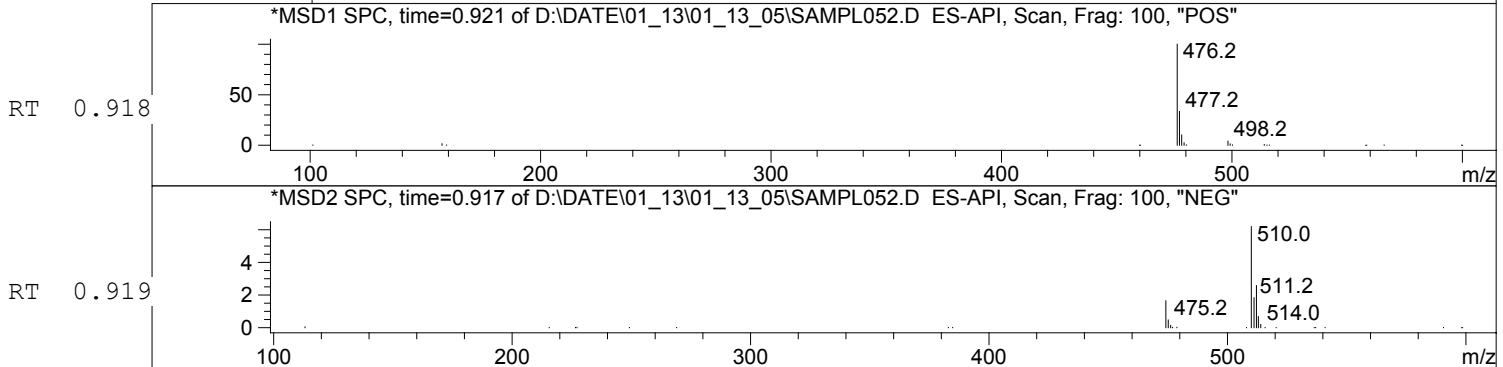
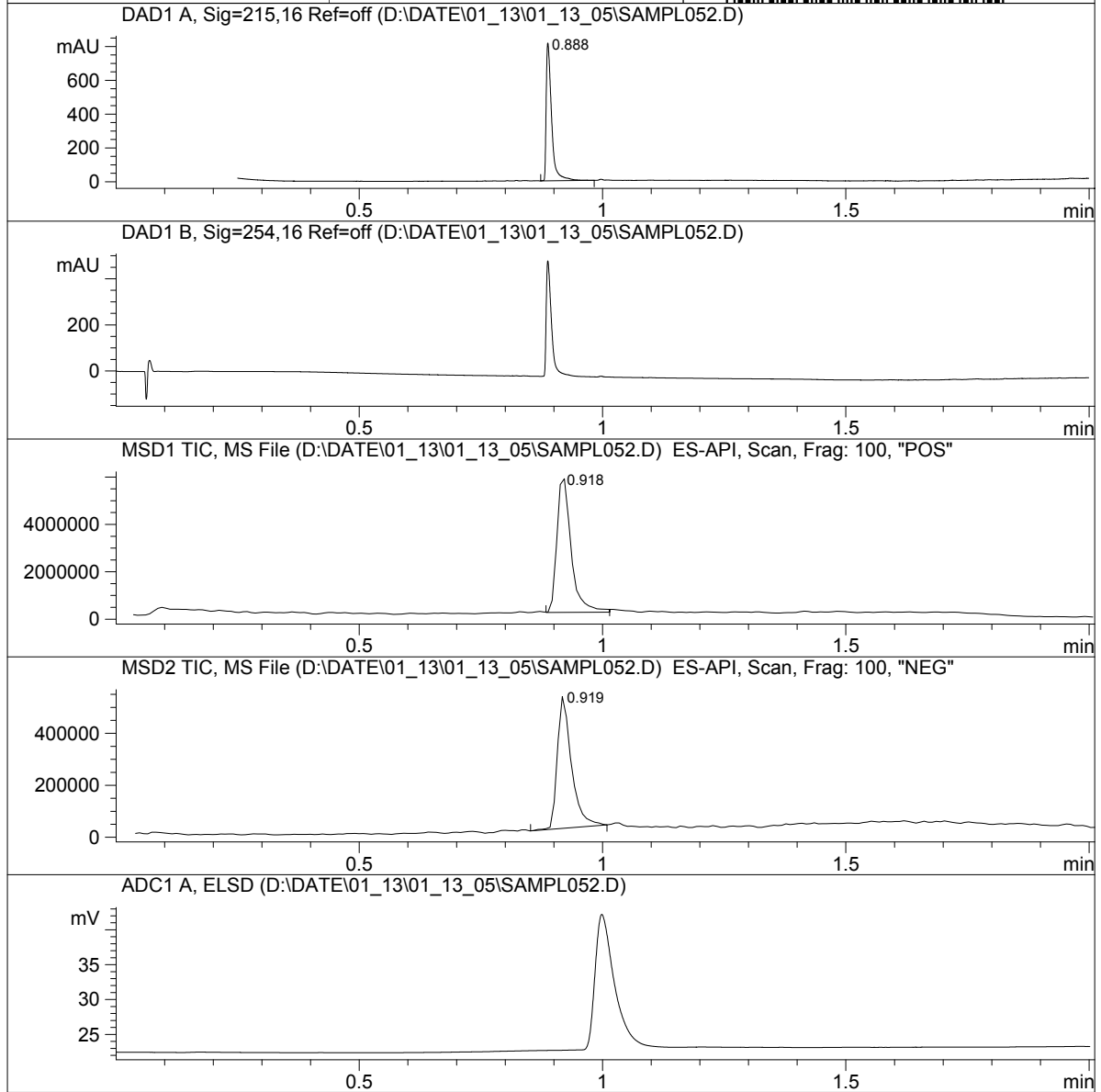
MaxPeak: 100.00%
Ret_Time: 0.888 min

4532099



Mol Wt 475.516
Exact Mass 475.13

| # | Time | Area% |
|---|-------|--------|
| 1 | 0.888 | 100.00 |



Compound ID: 14