Electronic Supporting Information **Part 1**

meso-Tetra(pentafluorophenyl)porphyrin as an Efficient Platform for Combinatorial Synthesis and the Selection of New Photodynamic Therapeutics using a Cancer Cell Line†

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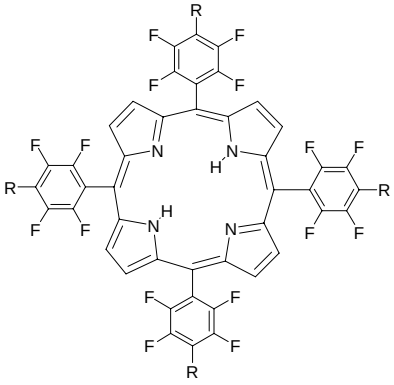
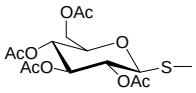
Dedicated to the memory of R. Bruce Merrifield, friend and colleague.

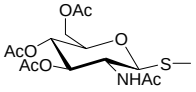


R_1 =



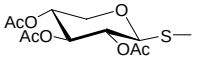
2,3,4,6-tetra-O-acetyl-glucosyl thioacetate = Glu

R_2 =



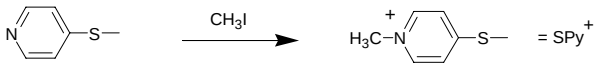
2-acetamido-3,4,6-tri-O-acetyl-
1-S-acetyl-2-deoxy-1-thioglucopyranose = Pyran

R_3 =



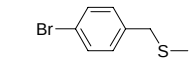
2,3,4-tri-O-acetyl-xylosyl thioacetate = Xyl

R_4 =



4-mercapto pyridine = SPy

R_5 =



(4-Bromo-phenyl)-methanethiol = S-BrBzyl

R_6 = $CH_3(CH_2)_4S$—

1-pentanethiol = S-Pen

R_7 = $CH_3(CH_2)_5S$—

1-hexanethiol = S-Hex

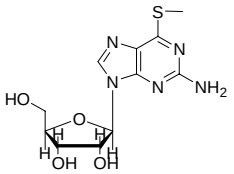
R_8 = $CH_3(CH_2)_7S$—

1-octanethiol = S-Oct

R_9 = F

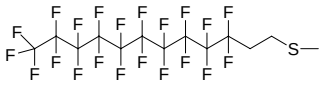
fluorine

R_{10}=



6-mercaptopurine riboside = Riboside

R_{11}=



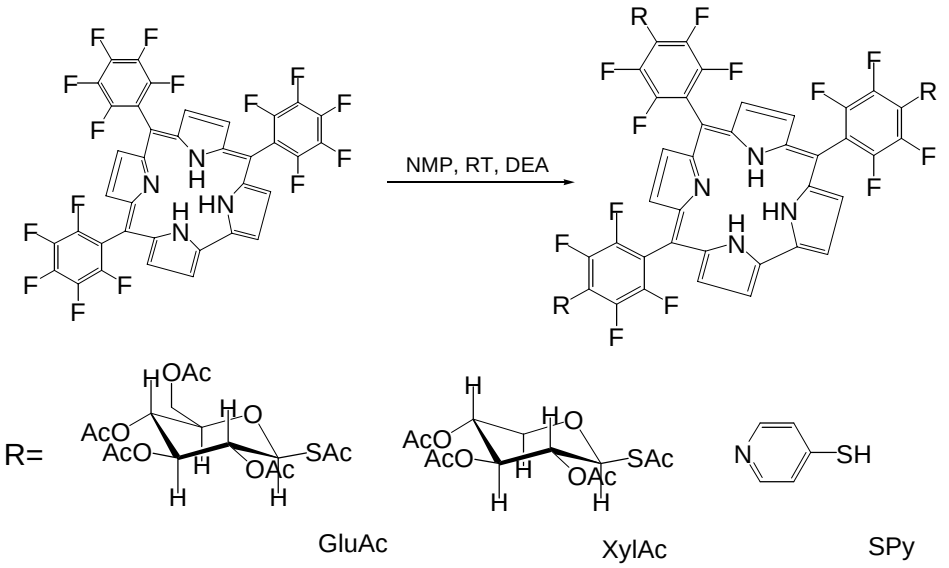
1H,1H,2H,2H-perfluorododecane-1-thiol = $C_{12}F_{21}$

Library 1 (21-member) = R_1, R_3, R_4

Library 2 (55-member) = R_1, R_2, R_3, R_4

Library 3 (666-member) = R_1, R_3, R_4, R_5, R_6, R_7, R_8, R_9

Scheme ESI-1. Core porphyrin and peripheral substituents.

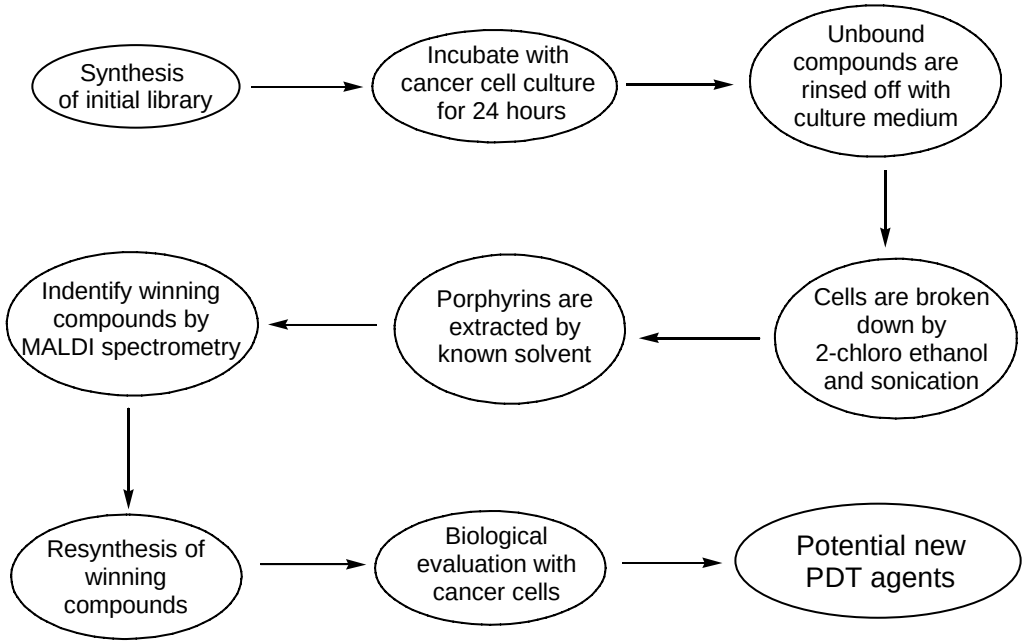


Scheme ESI-2: Solution phase combinatorial reaction scheme using tri(pentafluorophenyl)corrole. Protected glucose and xylose thioacetates, as well as thio pyridine are used as the nucleophiles. Three substituents would lead to an 18-member library (see mass spectrometry –Figure ESI-17).

Corrole Libraries: L4 and L5

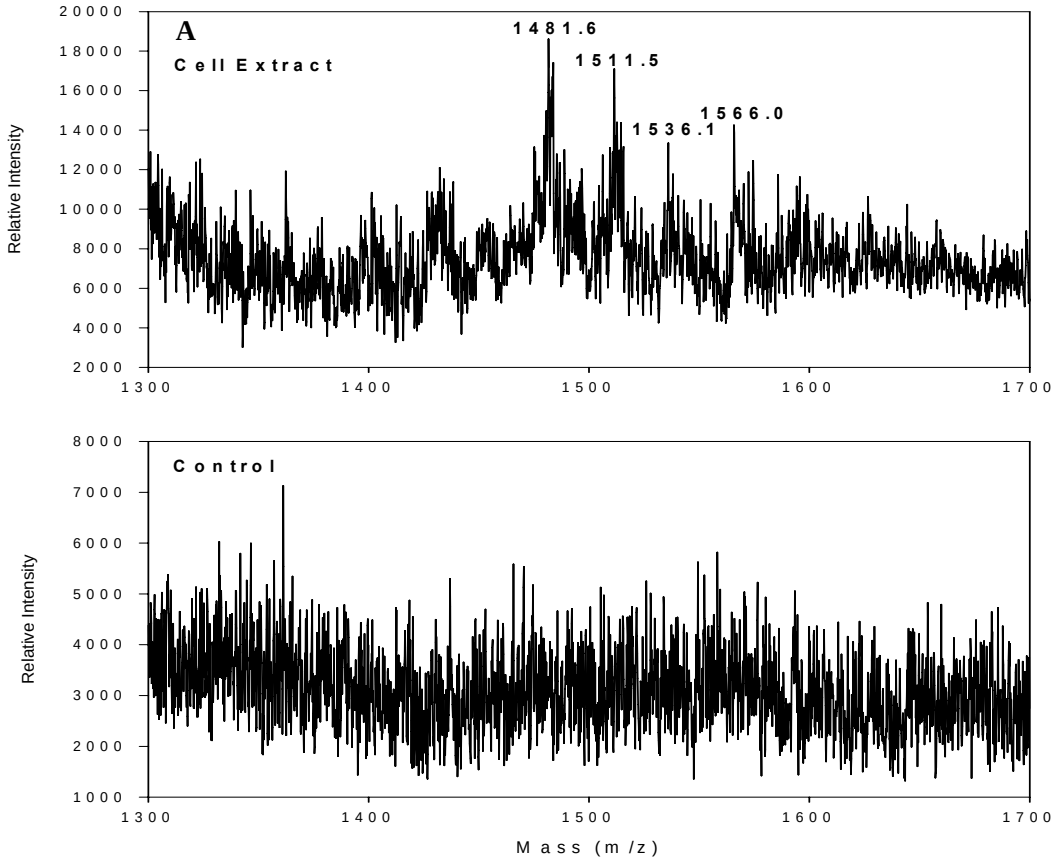
The efficiency of the nucleophilic coupling of thio moieties with p-fluorine atom of the perfluoro corrole was examined by using protected thio glucose. When essentially the same conditions employed for the porphyrin coupling are used (6.0 equivalents of thio glucose in DMF with 20 equivalents of DEA at room temperature for 24 hours), the major product is found to be the one where only the opposing perfluorophenyl groups have reacted. The tri-substituted derivative is formed in more than 60% yield when 9.0 equivalents of the thioglucose reagent are added to the $triPCF_{15}$ in DMF with 30 equivalents of DEA at room temperature and reacted for 48 h.

The synthesis of a small combinatorial library based on the $triPCF_{15}$ core (scheme ESI-2) was attempted using the conditions developed for the thioglucose substitution. First we employed 3 equivalents each of protected thioglucose, protected thioxylose and thiopentane. The reaction was done in DMF containing 40 equivalents of DEA at room temperature for 48h. Evaluation of the ESI MS spectra of the crude product mixture showed only partially substituted corrole systems. Increasing the quantity of the thio derivatives and increasing the reaction time do not significantly improve library yields, and thiopentane is found to be more reactive than the thio sugars. Neither thioimidazole nor thioundecanoicacid react with the $triPCF_{15}$ core to the extent as thioglucose as evidenced by ESI-MS spectra, which indicated a distribution of mono, di and tri substituted corrole-glucose systems. Replacing DMF with N-methylpyrrolidone (NMP) and examining the competition between thioglucose and thiopyridine still results in mainly the glycosylated derivatives.



Scheme ESI-3. Strategy of selection of winning compounds using a human breast cancer cell line (MDA-MB-231).

Identification of selected compounds by MALDI-MS. The noise in the MALDI spectra is largely due to both instrumental noise and some small amount of methanol-soluble compounds extracted along with the porphyrins. This selection assay was repeated three times with the same results. No attempt was made to purify the porphyrins from the cell extract to avoid losing or missing some compounds. The total amount of porphyrins extracted from the cancer cells, as estimated by ultraviolet-visible spectra is typically on the order of 10 μg/0.2 mL. At this stage of the research program, we do not know if there are any bio-conjugated porphyrins present which would manifest themselves as species with unknown molar mass.



B. Winning Compounds

Major Peaks

1481.6 Glu / Xyl / SPy / SPy (2 isomers)

1511.6 Glu / Glu / SPy / SPy (2 isomers)

Minor Peaks

1536.1 Glu / Xyl / Xyl / SPy (2 isomers)

1566.0 Glu / Glu / Xyl / SPy (2 isomers)

C

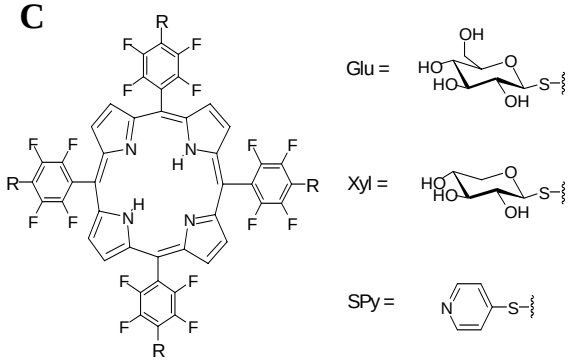


Figure ESI-1. Selection of winning compounds from human breast cancer (MDA-MB-231) cells. (A) MALDI-MS spectra of cell extract with library and control. The spectra are representative for more than 3 separate experiments. (B) Winning compounds determined by molecular weights. (C) The structures of winning compounds.

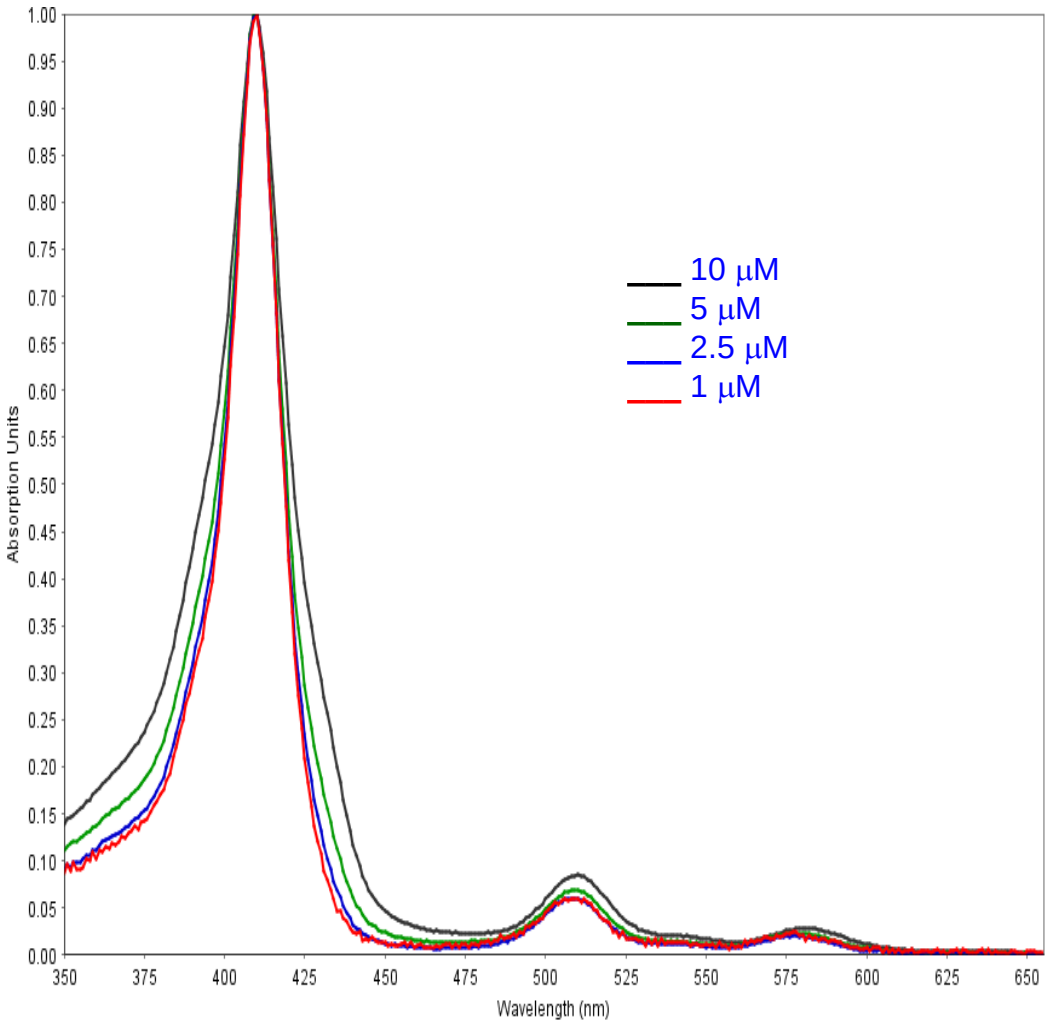


Figure ESI-2: Normalized absorption spectra for varying concentrations of Glu/Glu/Glu/Glu in aqueous PBS shows that this compound begins to aggregate at 5-10 μM.

Mass Spectrometry of Porphyrin Libraries

L1. 21-member library with GluAc, XylAc, SPy

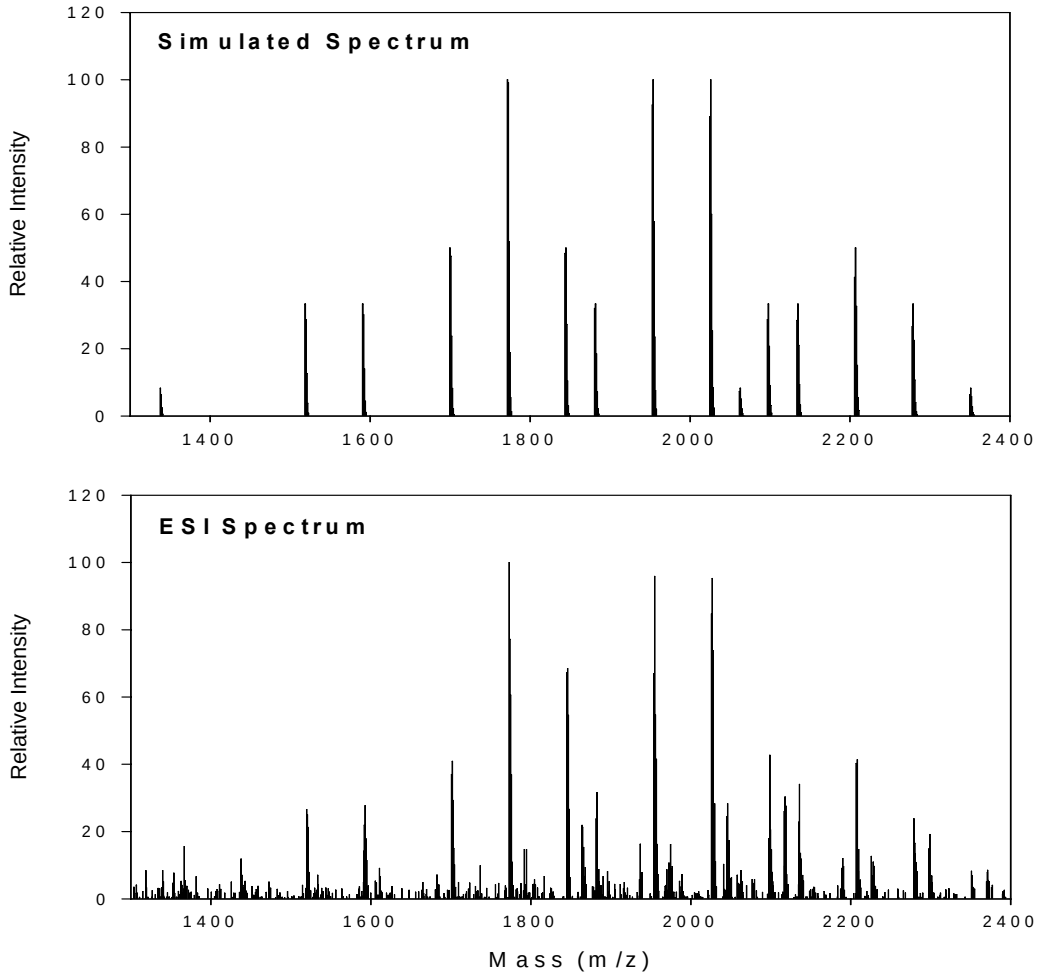


Figure ESI-3. Simulated (top) and experimental ESI-MS (bottom) spectra of 21-memberporphyrin library (15 isobaric peaks expected) with acetyl protected sugar moieties and thiopyridine: R= GluAc, XylAc, SPy. The actual ESI-MS spectrum is typically of more than three separate preparations.

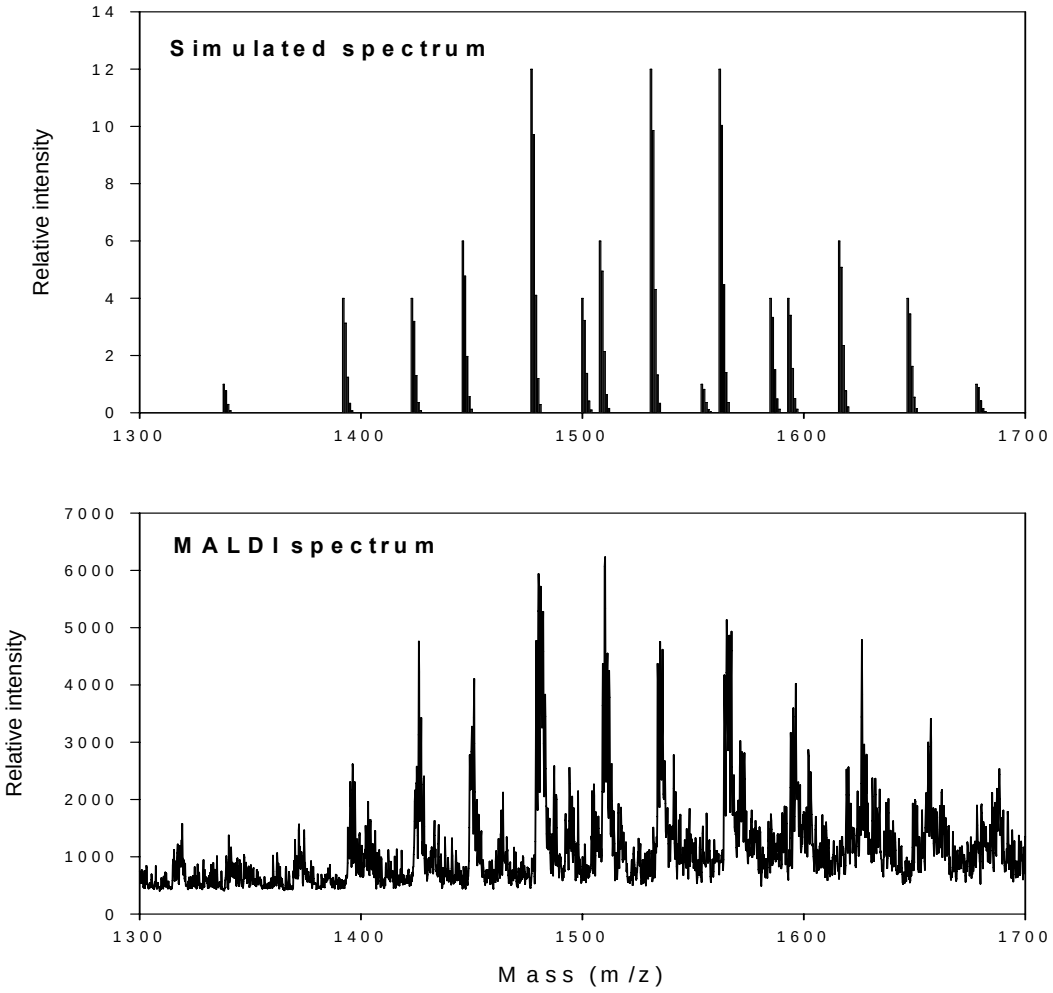


Figure ESI-4. Simulated (top) and experimental MALDI-MS (bottom) spectra of the same 21-member porphyrin library as in figure ESI-3, R= Glu, Xyl, SPy, (15 isobaric peaks expected) but with unprotected sugar moieties (Glu, Xyl, SPy). The MALDI-MS spectrum is representative of four separate preparations.

L2. 55-member library with GluAc, XylAc, SPy, PyranAc

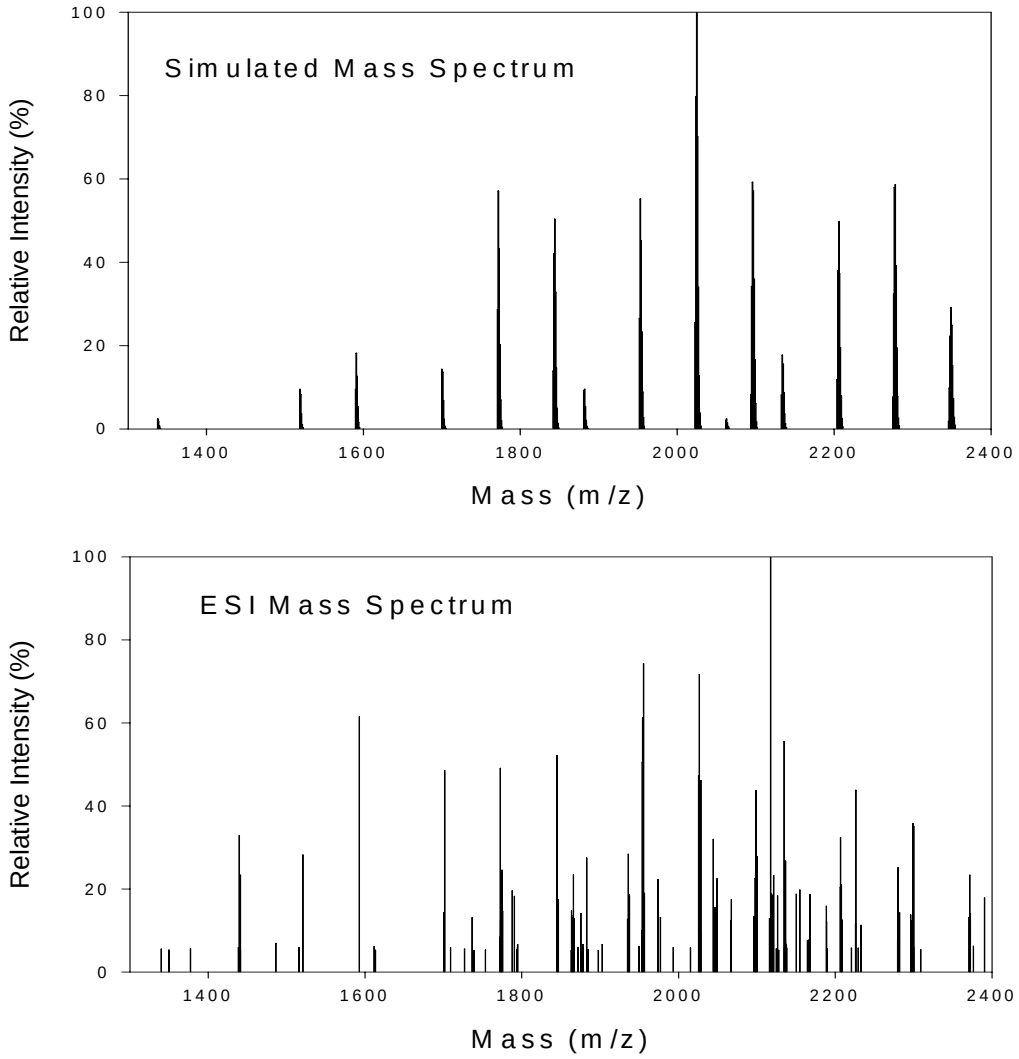


Figure ESI-5. Simulated mass spectrum (top) and ESI mass spectrum (bottom) of 55- member solution-phase combinatorial porphyrin library, R=GluAc, XylAc, SPy, PyranAc. 35 isobaric peaks are expected.

L3. 666 member library with R= GluAc, XylAc, SPy, SPen, SHex, SOct, SBrBzyl, F

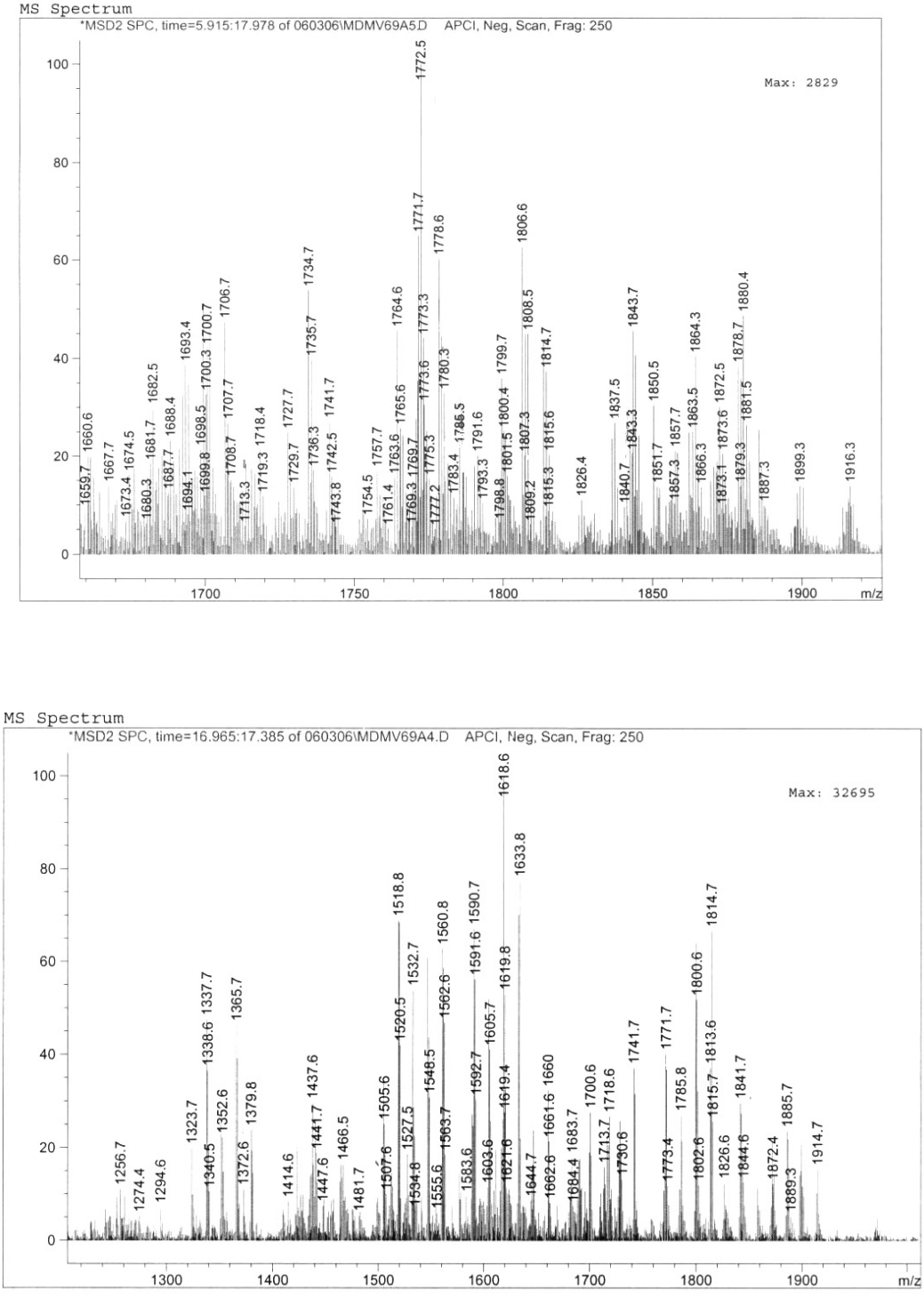


Figure ESI-6: ESI-MS of selected fractions of 666-combinatorial porphyrin library, HPLC fraction 1 (top) and 2 (bottom).

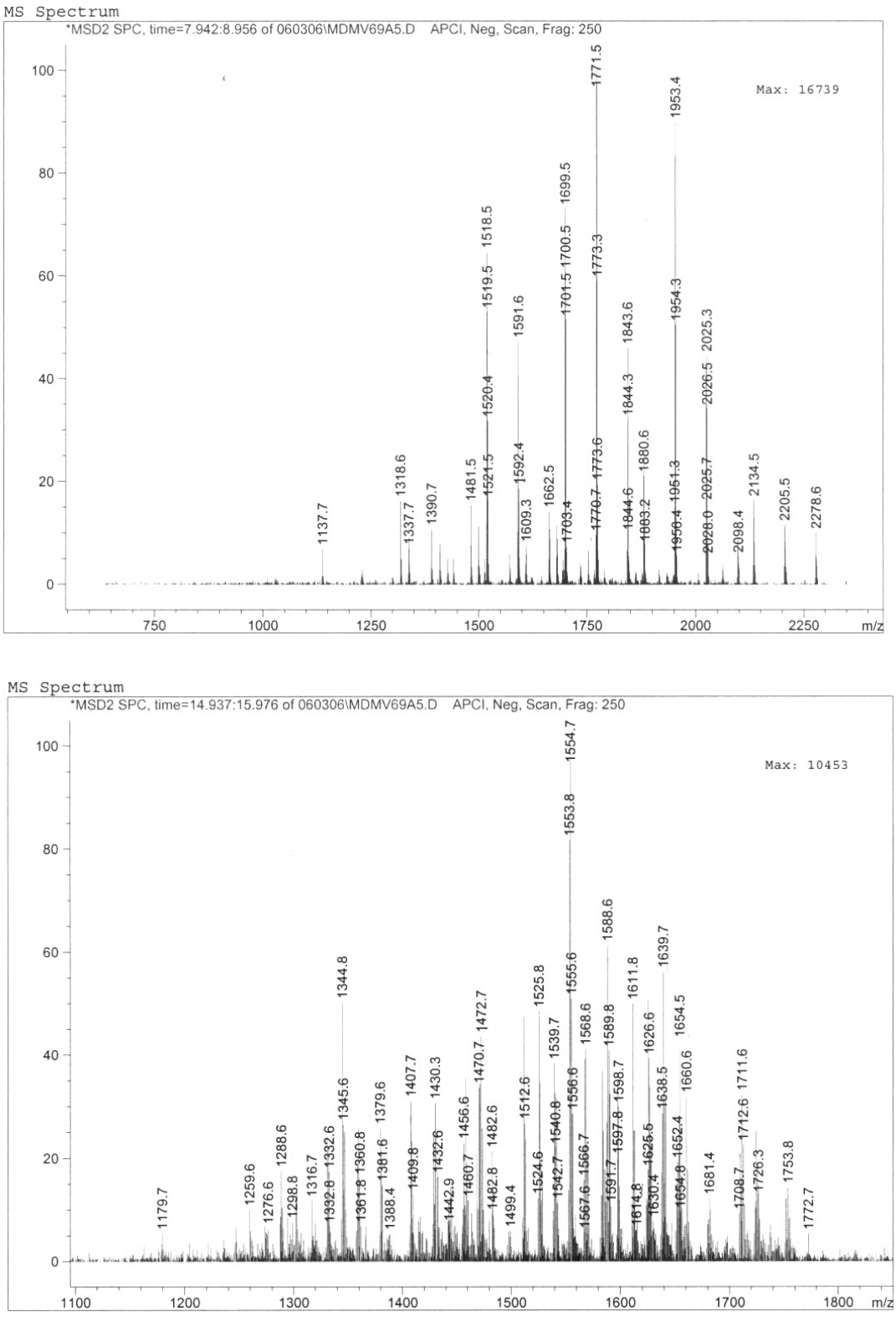


Figure ESI-7: ESI-MS of selected fractions of 666-combinatorial porphyrin library, HPLC fraction 3 (top) and 4 (bottom).

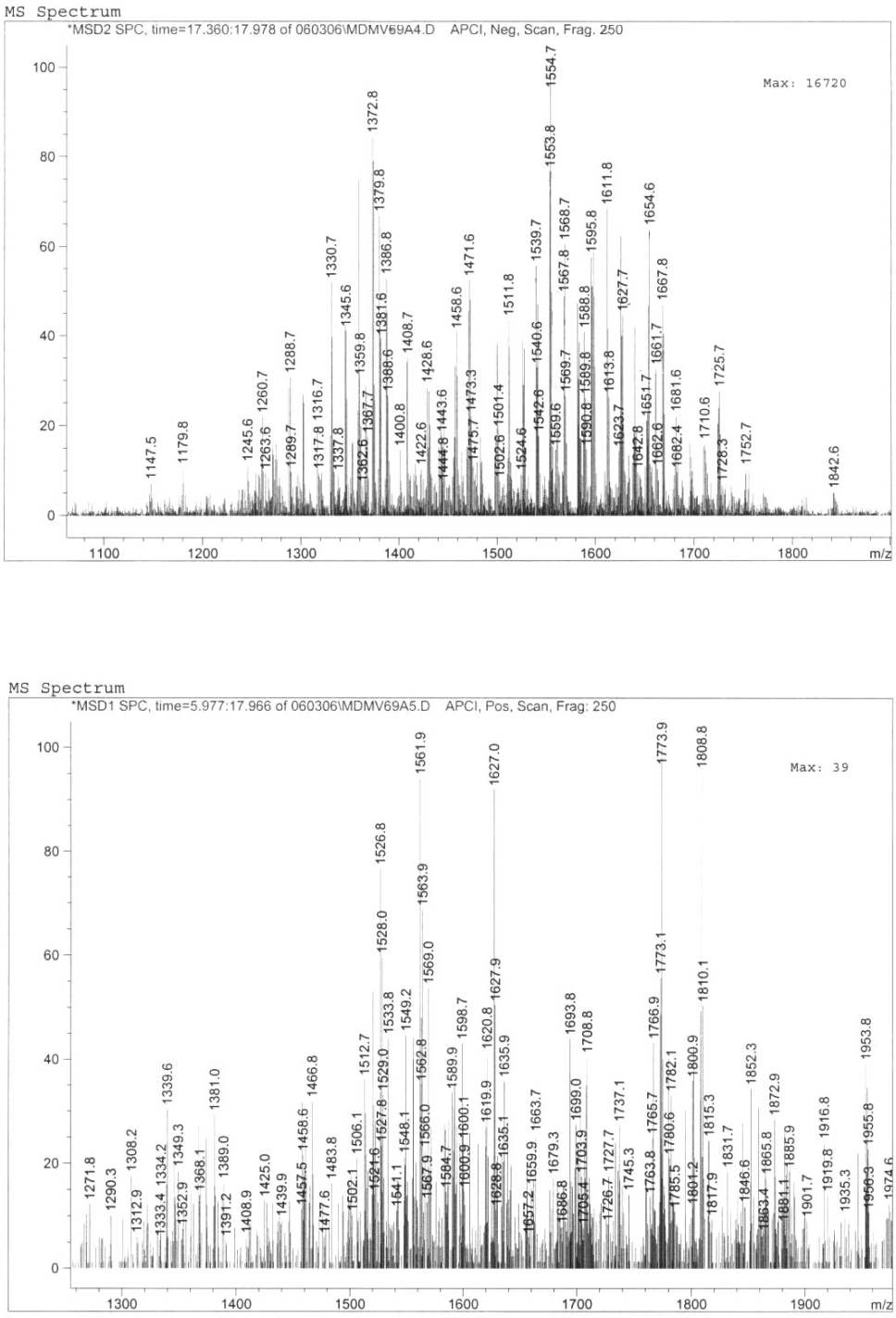
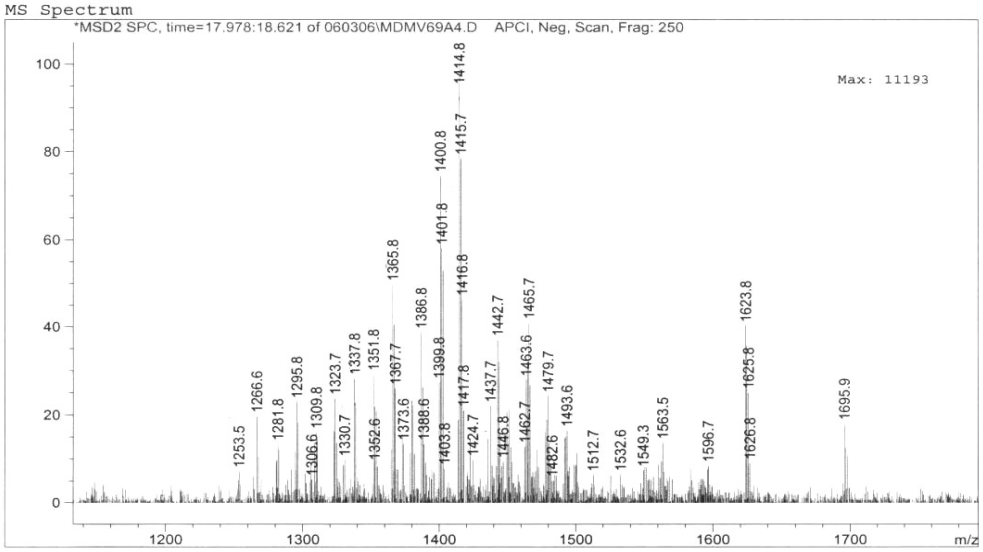


Figure ESI-8: ESI-MS of selected fractions of 666-combinatorial porphyrin library, HPLC fraction 5 (top) and 6 (bottom).



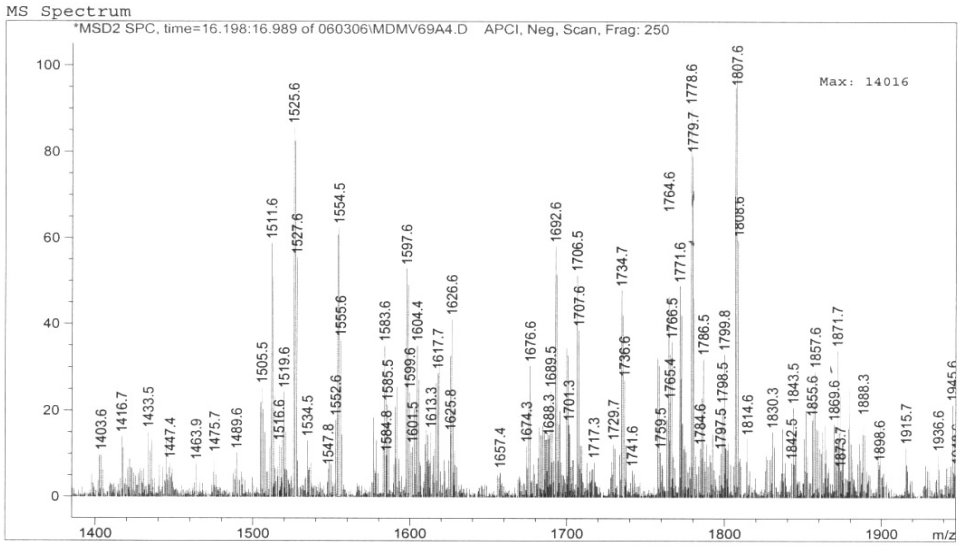


Figure ESI-9: ESI-MS of selected fractions of 666-combinatorial porphyrin library, HPLC fraction 7 (top) and 8 (bottom).

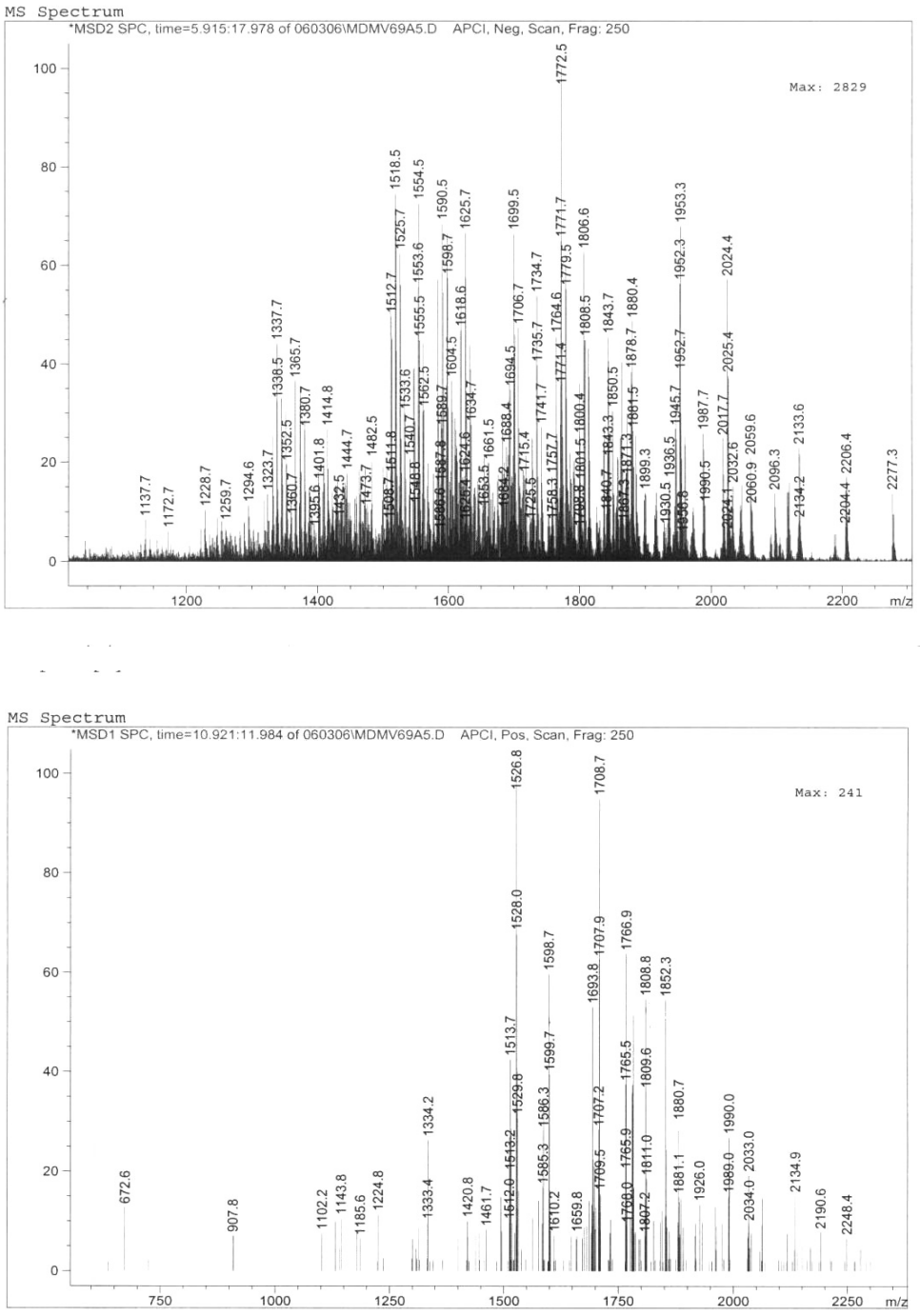


Figure ESI-10: ESI-MS of selected fractions of 666-combinatorial porphyrin library, HPLC fraction 9 (top) and 10 (bottom).

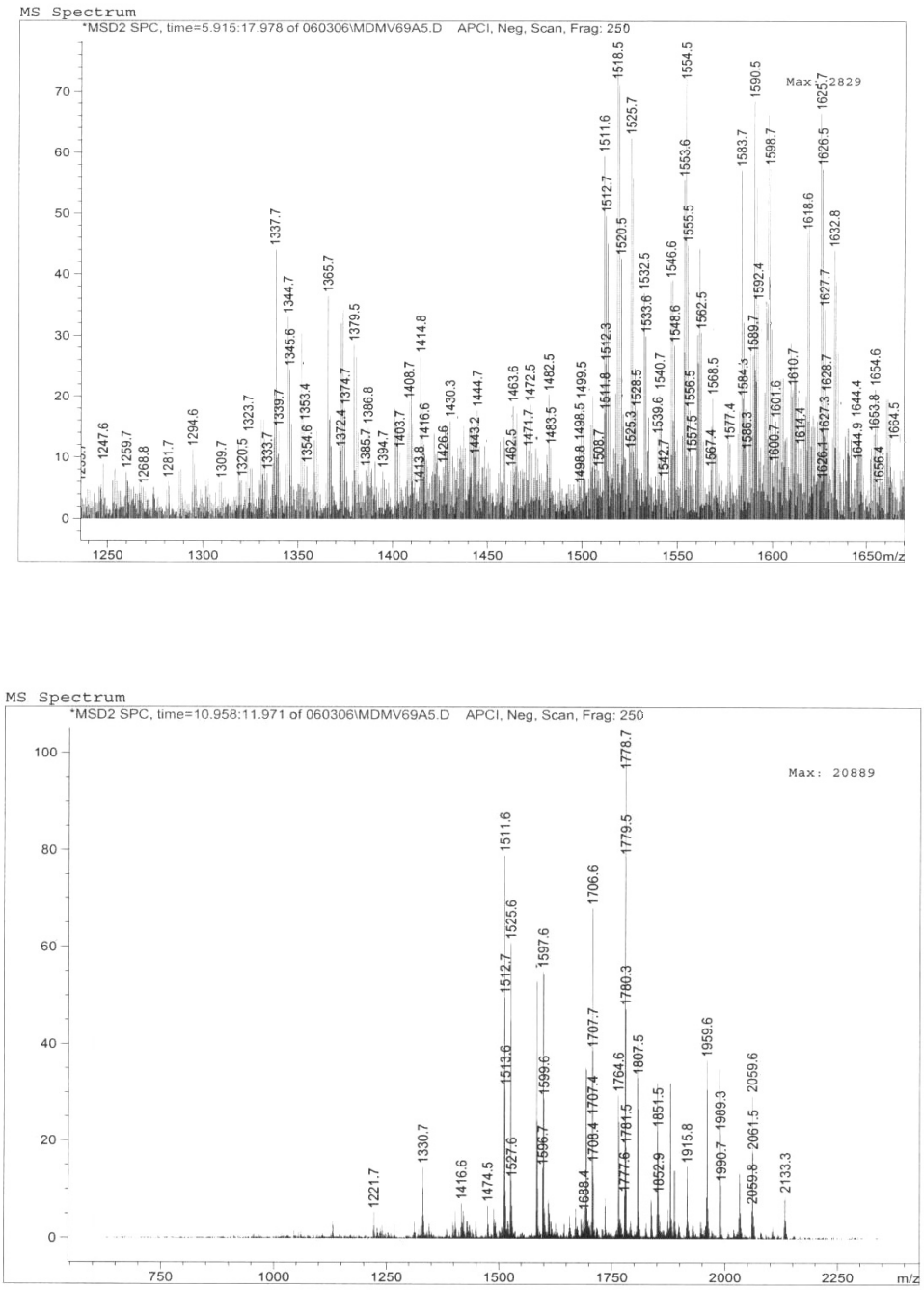


Figure ESI-11: ESI-MS of selected fractions of 666-combinatorial porphyrin library, HPLC fraction 11 (top) and 12 (bottom).

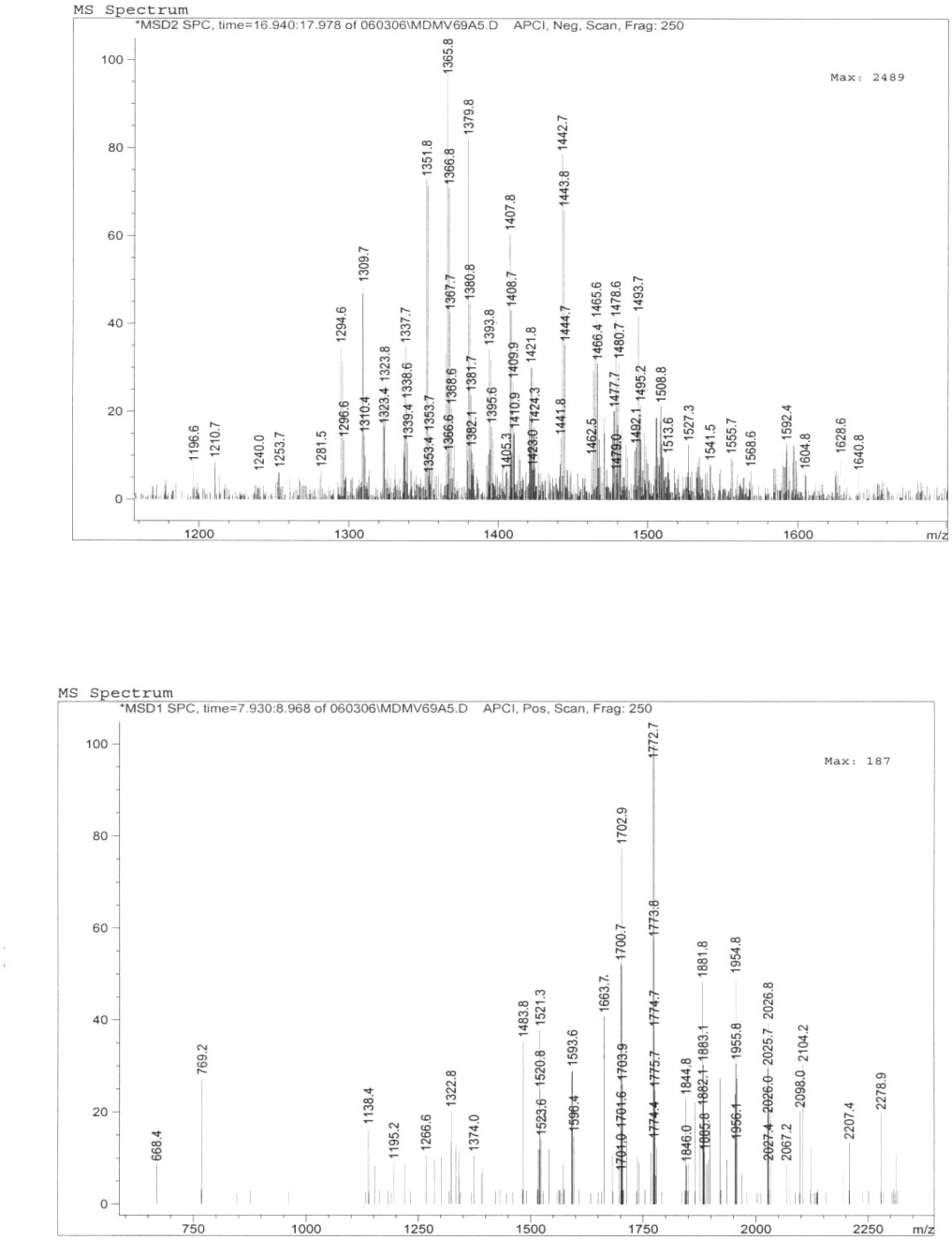


Figure ESI-12: ESI-MS of selected fractions of 666-combinatorial porphyrin library, HPLC fraction 13 (top) and 14 (bottom).

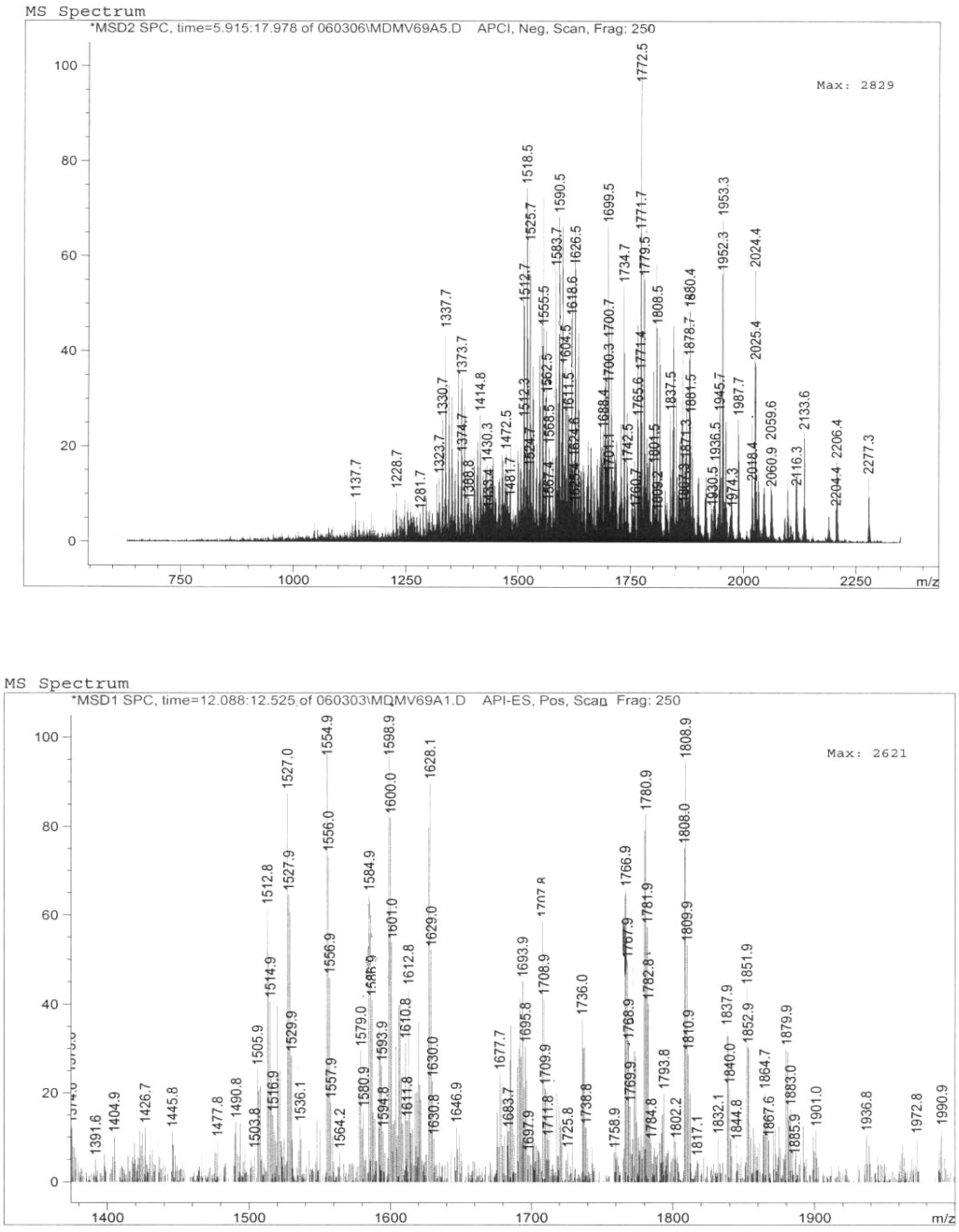


Figure ESI-13: ESI-MS of selected fractions of 666-combinatorial porphyrin library, HPLC fraction 15 (top) and 16 (bottom).

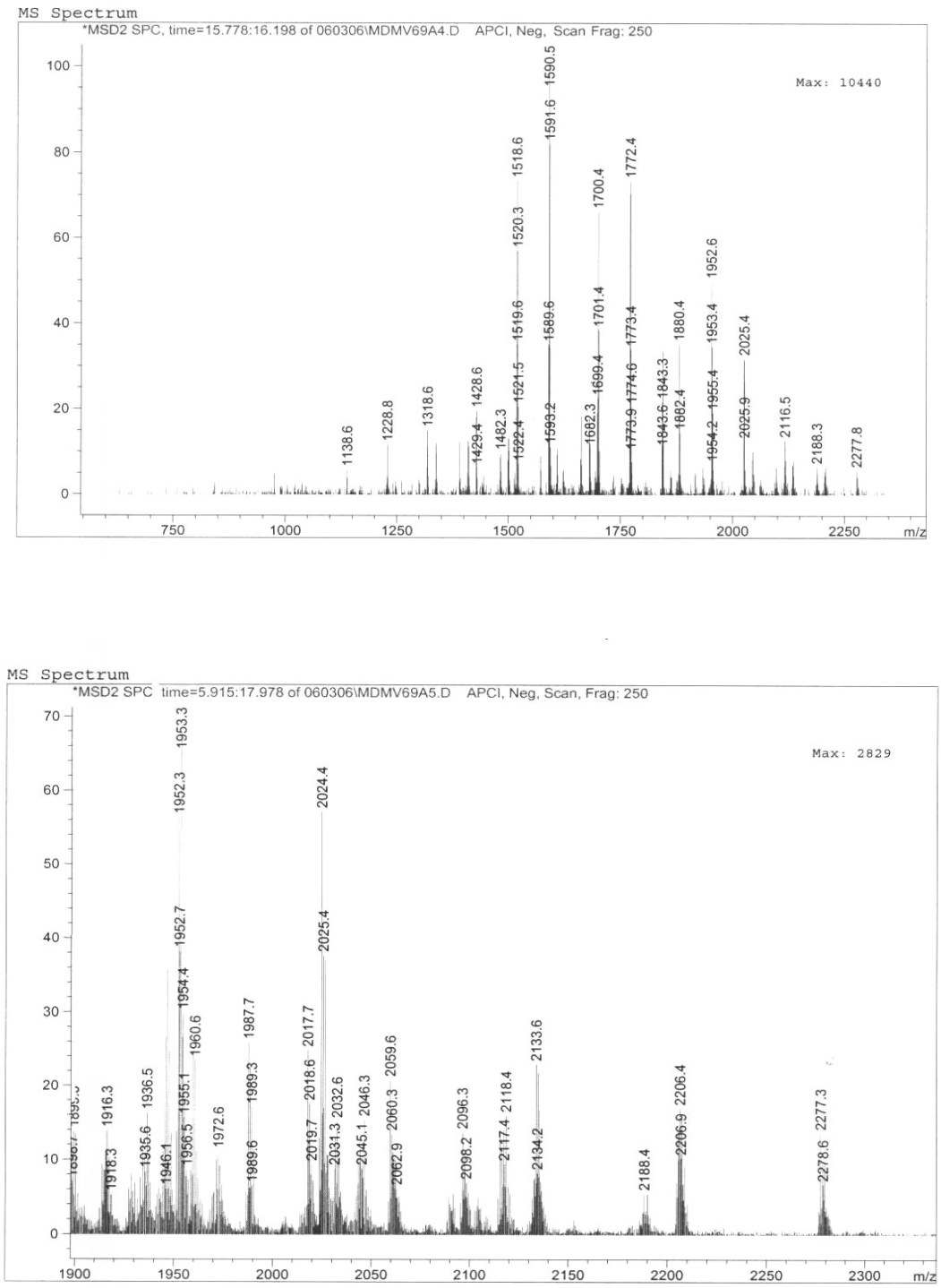


Figure ESI-14: ESI-MS of selected fractions of 666-combinatorial porphyrin library, HPLC fraction 17 (top) and 18 (bottom).

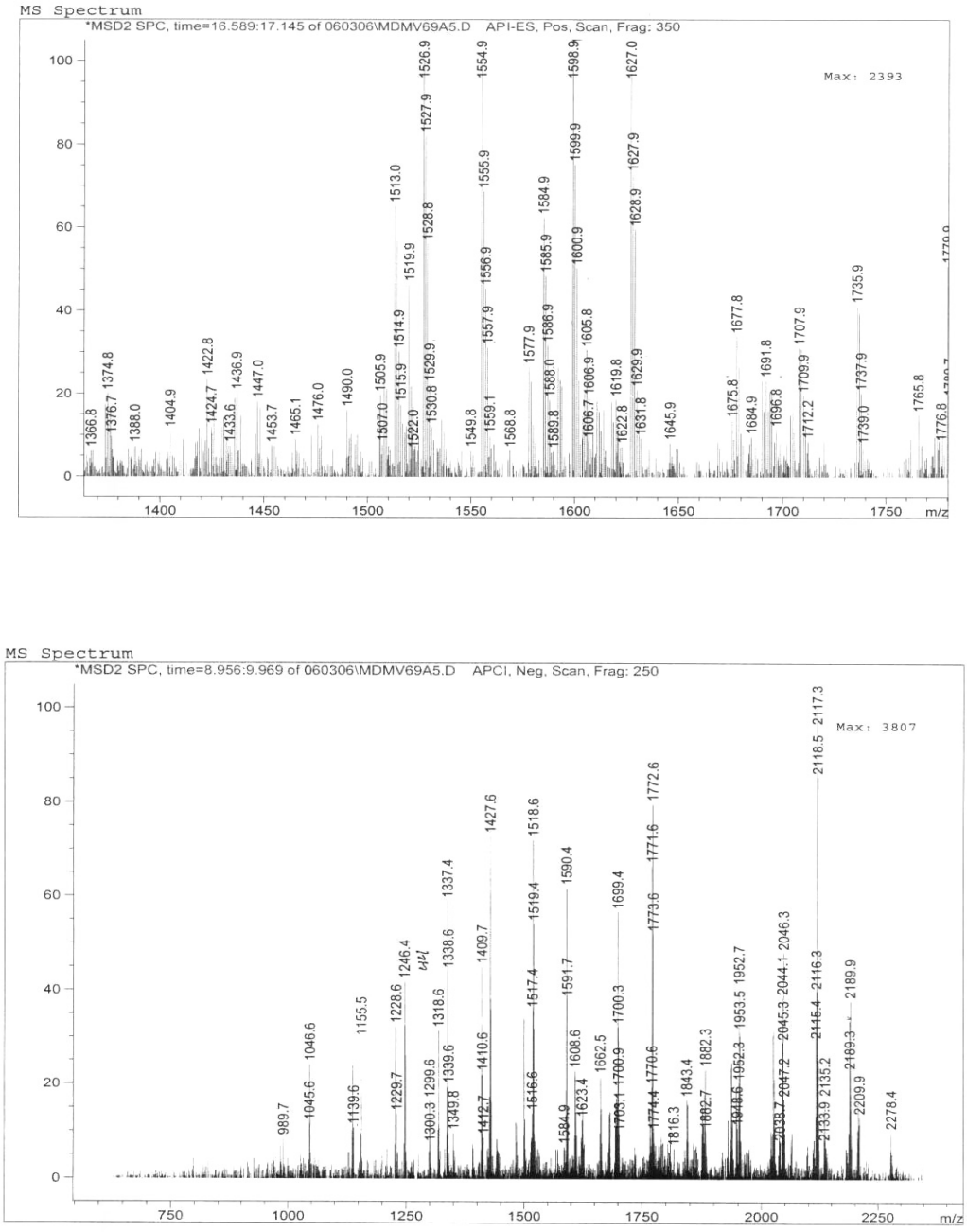


Figure ESI-15: ESI-MS of selected fractions of 666-combinatorial porphyrin library, HPLC fraction 19 (top) and 20 (bottom).

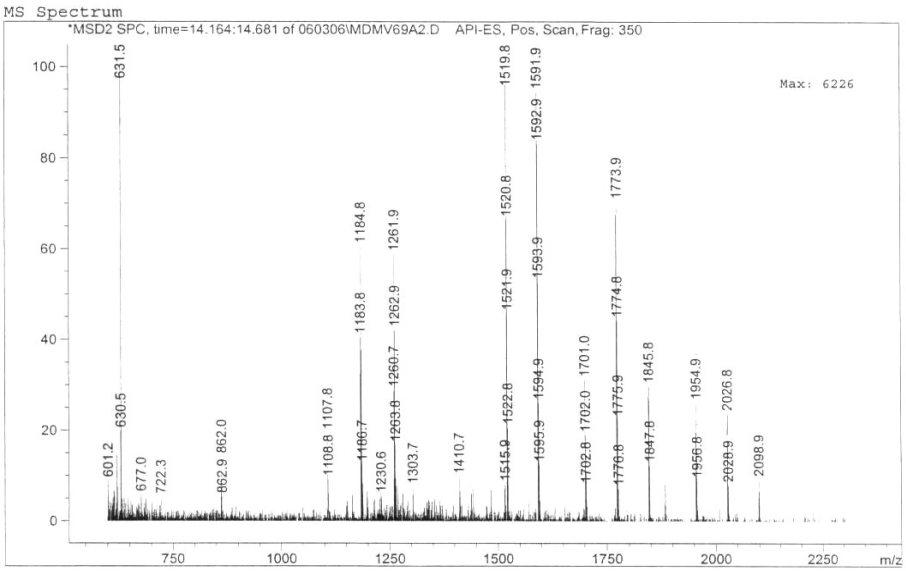


Figure ESI-16: ESI-MS of selected fractions of 666-combinatorial porphyrin library, HPLC fraction 21.

Table ESI-1. List of compounds identified by ESI-MS from the possible 330 isobaric species of the 666-porphyrin library. (Only 15 compounds were not detected directly in the ESI-MS, but out of which 14 can be identified by considering them as the Na/Cl/K/formate adducts.)

5,10,15,20		MW
1	F/F/F/F - not detected at all	974
2	F/F/F/SPen –only Na adduct detected	1058
3	F/F/F/SPy	1065
4	F/F/F/SHex	1072
5	F/F/F/SOct -only K adduct detected	1100
6	F/F/SPen/SPen	1142
7	F/SPy/F/SPen	1149
8	F/SPy/F/SPy	1156
9	F/F/SPen/SHex	1156
10	F/F/F/SBrBzyl	1157
11	F/F/SPy/SHex	1163
12	F/F/SHex/SHex	1170
13	F/SPen/F/SOct	1184
14	F/F/SPy/SOct	1191
15	F/F/SHex/SOct	1198
16	F/F/SOct/Soct -only Na adduct detected	1226
17	F/SPen/SPen/Spen -only Na adduct detected	1226
18	F/SPy/SPen/SPen -only formate adduct detected	1233
19	F/SPen/SHex/SPen	1240
20	F/SPy/SPy/SPen	1240
21	F/SPen/F/SBrBzyl	1241
22	F/F/F/XylAc	1246
23	F/SPy/SPen/SHex	1247
24	F/SPy/SPy/SPy	1247

25	F/F/SPy/SbrBzyl - only Na adduct detected	1248
26	F/SPy/SPy/SHex	1254
27	F/SHex/SPen/SHex	1254
28	F/F/SHex/SBrBzyl	1255
29	F/SPy/SHex/SHex	1261
30	F/SPen/SPen/SOct	1268
31	F/SHex/SHex/SHex	1268
32	F/SPy/SOct/SPen	1275
33	F/SPen/SOct/SHex	1282
34	F/SPy/SPy/SOct	1282
35	F/F/SOct/SBrBzyl	1283
36	F/SHex/SPy/SOct	1289
37	F/SHex/SHex/SOct	1296
38	F/SPen/SOct/SOct	1310
39	SPen/SPen/SPen/SPen	1310
40	F/SPy/SOct/SOct	1317
41	SPy/SPen/SPen/SPen	1317
42	F/F/F/GluAc	1318
43	SPy/SPy/SPen/SPen	1324
44	F/SHex/SOct/SOct	1324
45	SPen/SPen/SPen/SHex	1324
46	F/SPen/SBrBzyl/SPen	1325
47	F/F/XylAc/SPen	1330
48	SPy/SPen/SHex/SPen	1331
49	SPy/SPy/SPy/SPen	1331
50	F/SPen/SPy/SBrBzyl	1332
51	F/XylAc/F/SPy	1337
52	SPy/SPen/SPy/SHex	1338
53	SPy/SPy/SPy/SPy	1338
54	SPen/SPen/SHex/SHex	1338
55	F/SPen/SHex/SBrBzyl	1339
56	F/SPy/SPy/SBrBzyl	1339
57	F/SBrBzyl/F/SBrBzyl	1340
58	F/XylAc/F/SHex	1344
59	SPy/SPen/SHex/SHex	1345
60	SPy/SPy/SPy/SHex	1345
61	F/SHex/SPy/SBrBzyl	1346
62	SPy/SHex/SPy/SHex	1352
63	SPen/SPen/SPen/SOct	1352
64	F/SOct/SOct/SOct	1352
65	SPen/SHex/SHex/SHex	1352
66	F/SHex/SBrBzyl/SHex	1353
67	SPy/SPen/SPen/SOct	1359
68	SPy/SHex/SHex/SHex	1359
69	SPen/SPen/SHex/SOct	1366
70	SPy/SPen/SPy/SOct	1366
71	SHex/SHex/SHex/SHex	1366
72	F/SPen/SOct/SBrBzyl	1367
73	F/XylAc/F/SOct	1372
74	SPy/SPy/SPy/SOct	1373
75	SPy/SHex/SPen/SOct	1373
76	F/SPy/SOct/SBrBzyl	1374
77	SPy/SPy/SHex/SOct	1380
78	SPen/SHex/SHex/SOct	1380
79	F/SOct/SHex/SBrBzyl	1381
80	SPy/SHex/SOct/SHex	1387
81	SPen/SOct/SPen/SOct	1394

82	SHex/SHex/SHex/SOct		1394
83	SPy/SPen/SOct/SOct		1401
84	F/F/GluAc/SPen		1402
85	SPy/SPy/SOct/SOct		1408
86	SPen/SOct/SHex/SOct		1408
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88	SPen/SPen/SPen/SBrBzyl		1409
89	F/GluAc/F/SPy		1409
90	F/XylAc/SPen/SPen		1414
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92	F/GluAc/F/SHex		1416
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96	SPen/SPen/SHex/SBrBzyl		1423
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104	F/SBrBzyl/SPy/SBrBzyl		1431
105	F/XylAc/SPy/SHex		1435
106	SPen/SOct/SOct/SOct		1436
107	SPen/SHex/SBrBzyl/SHex		1437
108	SPy/SHex/SPy/SBrBzyl		1437
109	F/SBrBzyl/SHex/SBrBzyl		1438
110	F/SHex/XylAc/SHex		1442
111	SPy/SOct/SOct/SOct		1443
112	SPy/SHex/SHex/SBrBzyl		1444
113	F/GluAc/F/SOct		1444
114	SHex/SOct/SOct/SOct		1450
115	SPen/SPen/SOct/SBrBzyl		1451
116	SHex/SHex/SHex/SBrBzyl		1451
117	F/SPen/XylAc/SOct		1456
118	SPy/SPen/SOct/SBrBzyl		1458
119	F/XylAc/SPy/SOct		1463
120	SPen/SHex/SOct/SBrBzyl		1465
121	SPy/SOct/SPy/SBrBzyl		1465
122	F/SOct/SBrBzyl/SBrBzyl		1466
123	F/XylAc/SOct/SHex		1470
124	SPy/SOct/SHex/SBrBzyl		1472
125	SOct/SOct/SOct/SOct		1478
126	SHex/SHex/SOct/SBrBzyl		1479
127	F/GluAc/SPen/SPen	-only Cl adduct detected	1486
128	SPen/SOct/SBrBzyl/SOct		1493
129	F/SPy/GluAc/SPen		1493
130	F/SOct/XylAc/SOct		1498
131	XylAc/SPen/SPen/SPen		1498
132	F/GluAc/SPy/SPy		1500
133	F/GluAc/SPen/SHex		1500
134	SPy/SOct/SOct/SBrBzyl		1500
135	F/GluAc/F/SBrBzyl		1501
136	XylAc/SPen/SPy/SPen		1505
137	F/SPy/GluAc/SHex		1507
138	SHex/SOct/SOct/SBrBzyl		1507
139	SPen/SBrBzyl/SPen/SBrBzyl		1508
140	XylAc/SPy/SPen/SPy		1512

141	XylAc/SPen/SPen/SHex	1512
142	F/SPen/XylAc/SBrBzyl	1513
143	F/GluAc/SHex/SHex	1514
144	SPy/SPen/SBrBzyl/SBrBzyl	1515
145	F/F/XylAc/XylAc	1518
146	XylAc/SPy/SHex/SPen	1519
147	XylAc/SPy/SPy/SPy	1519
148	F/SPy/XylAc/SBrBzyl	1520
149	SPen/SBrBzyl/SHex/SBrBzyl	1522
150	SPy/SPy/SBrBzyl/SBrBzyl	1522
151	F/SBrBzyl/SBrBzyl/SBrBzyl	1523
152	XylAc/SPen/SHex/SHex	1526
153	XylAc/SPy/SPy/SHex	1526
154	F/XylAc/SBrBzyl/SHex	1527
155	F/SPen/GluAc/SOct	1528
156	SPy/SHex/SBrBzyl/SBrBzyl	1529
157	XylAc/SHex/SPy/SHex	1533
158	F/GluAc/SPy/SOct	1535
159	SOct/SOct/SOct/SBrBzyl	1535
160	SHex/SHex/SBrBzyl/SBrBzyl	1536
161	XylAc/SHex/SHex/SHex	1540
162	XylAc/SPen/SPen/SOct	1540
163	F/SHex/GluAc/SOct	1542
164	XylAc/SPen/SPy/SOct	1547
165	SPen/SOct/SBrBzyl/SBrBzyl	1550
166	XylAc/SPy/SOct/SPy	1554
167	XylAc/SPen/SOct/SHex	1554
168	F/XylAc/SOct/SBrBzyl	1555
169	SPy/SBrBzyl/SOct/SBrBzyl	1557
170	XylAc/SPy/SHex/SOct	1561
171	SHex/SOct/SBrBzyl/SBrBzyl	1564
172	XylAc/SHex/SOct/SHex	1568
173	GluAc/SPen/SPen/SPen	1570
174	F/GluAc/SOct/SOct	1570
175	GluAc/SPen/SPy/SPen	1577
176	XylAc/SOct/SPen/SOct	1582
177	GluAc/SPy/SPen/SPy	1584
178	GluAc/SPen/SPen/SHex	1584
179	F/GluAc/SBrBzyl/SPen	1585
180	XylAc/SPy/SOct/SOct	1589
181	F/GluAc/F/XylAc	1590
182	GluAc/SPy/SHex/SPen	1591
183	GluAc/SPy/SPy/SPy	1591
184	F/GluAc/SPy/SBrBzyl	1592
185	SOct/SOct/SBrBzyl/SBrBzyl	1592
186	XylAc/SOct/SHex/SOct	1596
187	XylAc/SPen/SPen/SBrBzyl	1597
188	GluAc/SPy/SPy/SHex	1598
189	GluAc/SPen/SHex/SHex	1598
190	F/GluAc/SBrBzyl/SHex	1599
191	F/XylAc/SPen/XylAc	1602
192	XylAc/SPen/SPy/SBrBzyl	1604
193	GluAc/SPy/SHex/SHex	1605
194	SPen/SBrBzyl/SBrBzyl/SBrBzyl	1607
195	F/XylAc/SPy/XylAc	1609
196	XylAc/SPen/SBrBzyl/SHex	1611
197	XylAc/SPy/SBrBzyl/SPy	1611
198	F/SBrBzyl/XylAc/SBrBzyl	1612
199	GluAc/SPen/SOct/SPen	1612

200	GluAc/SHex/SHex/SHex	1612
201	SPy/SBrBzyl/SBrBzyl/SBrBzyl	1614
202	F/XylAc/SHex/XylAc	1616
203	XylAc/SPy/SHex/SBrBzyl	1618
204	GluAc/SPy/SOct/SPen	1619
205	SHex/SBrBzyl/SBrBzyl/SBrBzyl	1621
206	XylAc/SOct/SOct/SOct	1624
207	XylAc/SHex/SHex/SBrBzyl	1625
208	GluAc/SHex/SPen/SOct	1626
209	GluAc/SPy/SOct/SPy	1626
210	F/GluAc/SBrBzyl/SOct	1627
211	GluAc/SHex/SPy/SOct	1633
212	XylAc/SPen/SOct/SBrBzyl	1639
213	GluAc/SHex/SHex/SOct	1640
214	F/XylAc/XylAc/SOct	1644
215	XylAc/SOct/SPy/SBrBzyl	1646
216	SOct/SBrBzyl/SBrBzyl/SBrBzyl	1649
217	XylAc/SHex/SBrBzyl/SOct	1653
218	GluAc/SOct/SPen/SOct	1654
219	GluAc/SPy/SOct/SOct	1661
220	F/F/GluAc/GluAc	1662
221	GluAc/SOct/SHex/SOct	1668
222	GluAc/SPen/SPen/SBrBzyl	1669
223	F/GluAc/XylAc/SPen	1674
224	GluAc/SPy/SPen/SBrBzyl	1676
225	XylAc/SOct/SBrBzyl/SOct	1681
226	F/GluAc/SPy/XylAc	1681
227	GluAc/SPy/SPy/SBrBzyl	1683
228	GluAc/SPen/SBrBzyl/SHex	1683
229	F/GluAc/SBrBzyl/SBrBzyl	1684
230	XylAc/SPen/XylAc/SPen	1686
231	F/XylAc/GluAc/SHex	1688
232	GluAc/SHex/SPy/SBrBzyl	1690
233	XylAc/XylAc/SPy/SPen	1693
234	XylAc/SBrBzyl/SPen/SBrBzyl	1696
235	GluAc/SOct/SOct/SOct	1696
236	GluAc/SHex/SBrBzyl/SHex	1697
237	XylAc/SPen/XylAc/SHex	1700
238	XylAc/SPy/XylAc/SPy	1700
239	F/XylAc/SBrBzyl/XylAc	1701
240	XylAc/SPy/SBrBzyl/SBrBzyl	1703
241	SBrBzyl/SBrBzyl/SBrBzyl/SBrBzyl	1706
242	XylAc/XylAc/SPy/SHex	1707
243	XylAc/SHex/SBrBzyl/SBrBzyl	1710
244	GluAc/SPen/SOct/SBrBzyl	1711
245	XylAc/SHex/XylAc/SHex	1714
246	F/GluAc/SOct/XylAc	1716
247	GluAc/SPy/SBrBzyl/SOct	1718
248	GluAc/SHex/SOct/SBrBzyl	1725
249	XylAc/XylAc/SPen/SOct	1728
250	XylAc/XylAc/SPy/SOct	1735
251	XylAc/SOct/SBrBzyl/SBrBzyl	1738
252	XylAc/SHex/XylAc/SOct	1742
253	F/GluAc/GluAc/SPen - only Na adduct detected	1746
254	F/GluAc/SPy/GluAc	1753

255	GluAc/SOct/SOct/SBrBzyl	1753
256	GluAc/XylAc/SPen/SPen	1758
257	F/GluAc/GluAc/SHex	1760
258	GluAc/XylAc/SPen/SPy	1765
259	GluAc/SPen/SBrBzyl/SBrBzyl	1768
260	XylAc/XylAc/SOct/SOct	1770
261	GluAc/XylAc/SPen/SHex	1772
262	GluAc/SPy/XylAc/SPy	1772
263	F/GluAc/SBrBzyl/XylAc	1773
264	GluAc/SBrBzyl/SPy/SBrBzyl	1775
265	GluAc/XylAc/SPy/SHex	1779
266	GluAc/SHex/SBrBzyl/SBrBzyl	1782
267	XylAc/XylAc/SPen/SBrBzyl	1785
268	GluAc/SHex/XylAc/SHex	1786
269	F/GluAc/SOct/GluAc	1788
270	F/XylAc/XylAc/XylAc	1790
271	XylAc/SPy/XylAc/SBrBzyl	1792
272	XylAc/SBrBzyl/SBrBzyl/SBrBzyl	1795
273	XylAc/SHex/XylAc/SBrBzyl	1799
274	GluAc/SPen/XylAc/SOct -only K adduct detected	1800
275	GluAc/XylAc/SPy/SOct	1807
276	GluAc/SBrBzyl/SOct/SBrBzyl	1810
277	GluAc/XylAc/SHex/SOct	1814
278	XylAc/SOct/XylAc/SBrBzyl	1827
279	GluAc/SPen/GluAc/SPen -only Cl adduct detected	1830
280	GluAc/SPy/GluAc/SPen	1837
281	GluAc/SOct/XylAc/SOct	1842
282	GluAc/GluAc/SPy/SPy	1844
283	GluAc/SPen/GluAc/SHex	1844
284	F/GluAc/GluAc/SBrBzyl	1845
285	GluAc/SPy/GluAc/SHex	1851
286	GluAc/SPen/XylAc/SBrBzyl	1857
287	GluAc/SHex/GluAc/SHex	1858
288	F/XylAc/GluAc/XylAc	1862
289	GluAc/XylAc/SBrBzyl/SPy	1864
290	GluAc/SBrBzyl/SBrBzyl/SBrBzyl	1867
291	GluAc/SHex/XylAc/SBrBzyl	1871
292	GluAc/GluAc/SPen/SOct	1872
293	XylAc/XylAc/XylAc/SPen	1874
294	GluAc/GluAc/SPy/SOct	1879
295	XylAc/XylAc/XylAc/SPy	1881
296	XylAc/SBrBzyl/XylAc/SBrBzyl	1884
297	GluAc/SHex/GluAc/SOct	1886
298	XylAc/XylAc/XylAc/SHex	1888
299	GluAc/XylAc/SOct/SBrBzyl	1899
300	GluAc/SOct/GluAc/SOct	1914
301	XylAc/XylAc/XylAc/SOct	1916
302	GluAc/SPen/GluAc/SBrBzyl - only Na adduct detected	1929
303	F/GluAc/XylAc/GluAc	1934
304	GluAc/SPy/GluAc/SBrBzyl	1936
305	GluAc/SHex/GluAc/SBrBzyl	1943
306	GluAc/XylAc/XylAc/SPen	1946
307	GluAc/XylAc/XylAc/SPy	1953
308	GluAc/XylAc/SBrBzyl/SBrBzyl	1956
309	GluAc/XylAc/SHex/XylAc	1960
310	GluAc/SOct/GluAc/SBrBzyl	1971

311	XylAc/XylAc/XylAc/SBrBzyl	1973
312	GluAc/XylAc/XylAc/SOct	1988
313	F/GluAc/GluAc/GluAc - only Na adduct detected	2006
314	GluAc/XylAc/GluAc/SPen	2018
315	GluAc/GluAc/XylAc/SPy	2025
316	GluAc/GluAc/SBrBzyl/SBrBzyl	2028
317	GluAc/GluAc/XylAc/SHex	2032
318	GluAc/XylAc/XylAc/SBrBzyl	2045
319	GluAc/GluAc/XylAc/SOct	2060
320	XylAc/XylAc/XylAc/XylAc	2062
321	GluAc/GluAc/GluAc/SPen -only formate adduct detected	2090
322	GluAc/GluAc/GluAc/SPy	2097
323	GluAc/GluAc/GluAc/SHex - only Cl adduct detected	2104
324	GluAc/XylAc/GluAc/SBrBzyl	2117
325	GluAc/GluAc/GluAc/SOct	2132
326	GluAc/XylAc/XylAc/XylAc	2134
327	GluAc/GluAc/GluAc/SBrBzyl	2189
328	GluAc/XylAc/GluAc/XylAc	2206
329	GluAc/GluAc/GluAc/XylAc	2278
330	GluAc/GluAc/GluAc/GluAc	2350

Table ESI-2. Abundance of each compound in core-centered libraries is not equivalent; for the 21-member library L-1.

R	% in library	% of cis-isomer	% of trans-isomer
Py / Py / Py / Py	1.23	/	/
Py / Py / Py / Xyl	4.94	/	/
Py / Py / Py / Glu	4.94	/	/
Py / Py / Xyl / Xyl	7.41	4.94	2.47
Py / Py / Glu / Xyl	14.81	9.88	4.94
Py / Py / Glu / Glu	7.41	4.94	2.47
Py / Xyl / Xyl / Xyl	4.94	/	/
Py / Glu / Xyl / Xyl	14.81	9.88	4. 94
Py / Glu / Glu / Xyl	14.81	9.88	4.94
Xyl / Xyl / Xyl / Xyl	1.23	/	/
Py / Glu / Glu / Glu	4.94	/	/
Glu / Xyl / Xyl / Xyl	4.94	/	/
Glu / Glu / Xyl / Xyl	7.41	4.94	2.47
Glu / Glu / Glu / Xyl	4.94	/	/
Glu / Glu / Glu / Glu	1.23	/	/

Mass Spectrometry of Corrole Libraries: L4 and L5

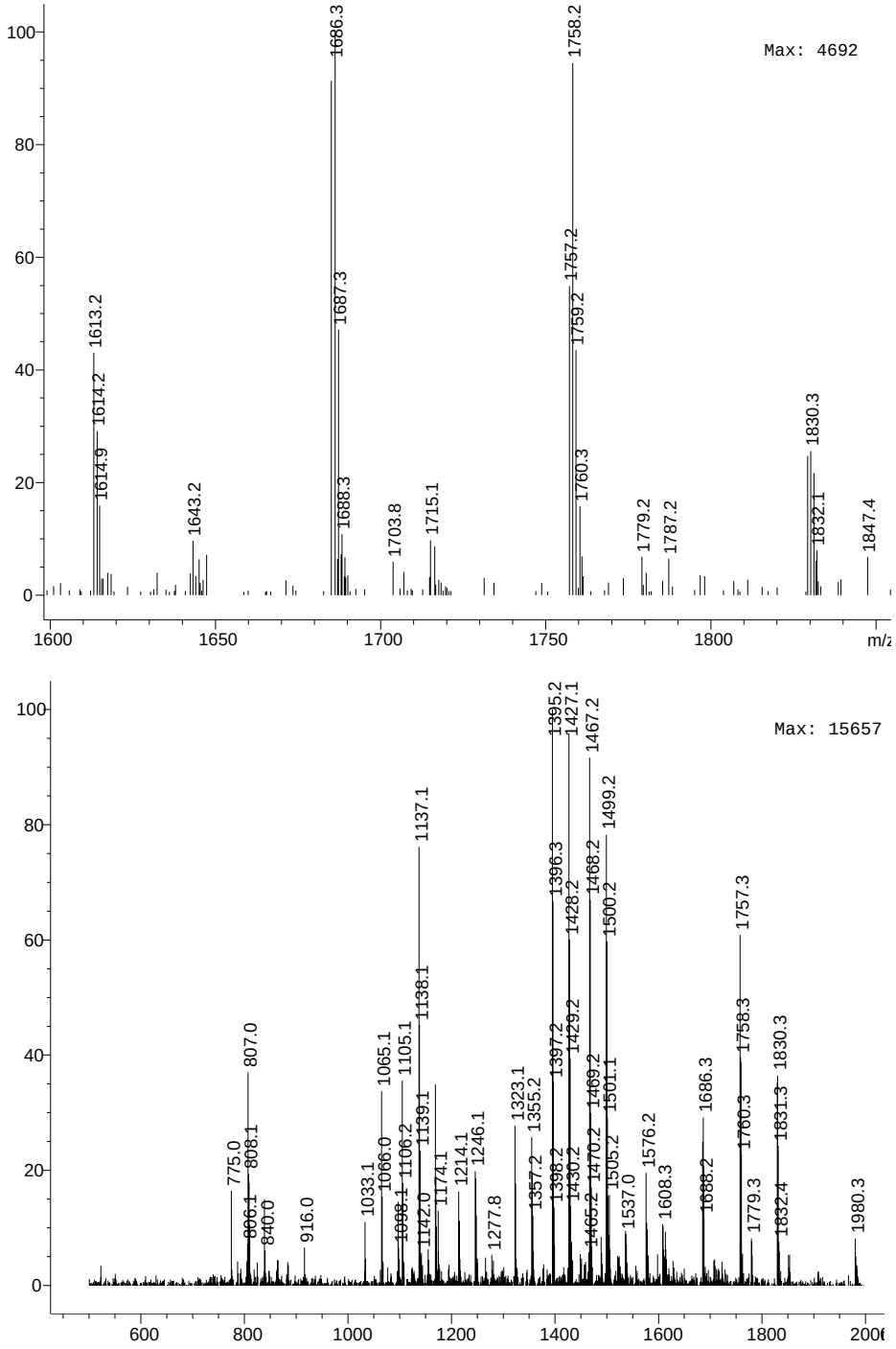


Figure ESI-17: ESI-MS of corrole libraries using **(A)** only glucose and xylose thioacetates where six compounds are expected, and **(B)** the two thiosugars as well as thio pyridine as the nucleophiles, where 18 compounds are expected. Since the isomers have the same molecular weights, the number of isobaric compounds for the library in A is four, and for the library in B is 10.

Table ESI-3. Possible compounds for the corrole libraries

GluAc/XylAc with possible incomplete substitution of the F

Compound #	**Substituents**	**m/z**
1	F/F/F	796
2/3	XylAc/F/F, F/XylAc/F	1068
4/5	GluAc/F/F, F/GluAc/F	1140
6/7	XylAc/XylAc/F, XylAc/F/XylAc	1340
8/9/10	GluAc/XylAc/F, GluAc/F/XylAc F/GluAc/XylAc	1412
11/12	GluAc/GluAc/F, GluAc/F/GluAc	1484
13	XylAc/XylAc/XylAc	1612
14/15	GluAc/XylAc/XylAc, XylAc/GluAc/XylAc	1684
16/17	GluAc/GluAc/XylAc, GluAc/XylAc/GluAc	1756
18	GluAc/GluAc/GluAc	1828

The highlighted compounds were found in the MS analysis, thus indicating that the target 6-member library was synthesized with reasonable yield.

Table ESI-4. *GluAc/XylAc and SPy with possible incomplete substitution of the F*

Compound #	**Substituents**	**m/z**
1	F/F/F/	796
2/3	SPy/F/F, F/SPy/F	887
4/5	SPy/SPy/F, SPy/F/SPy	978
6/7	XylAc/F/F, F/XylAc/F	1068
8	SPy/SPy/SPy	1069
9/10	GluAc/F/F, F/ GluAc/F	1140
11/12/13	XylAc/SPy/F, XylAc/F/SPy, F/XylAc/SPy	1159
14/15/16	GluAc/SPy/F, GluAc/F/SPy, F/GluAc/SPy	1231
17/18	XylAc/SPy/SPy, SPy/XylAc/SPy	1250
19/20	GluAc/SPy/SPy, SPy/GluAc/SPy	1322
21/22	XylAc/XylAc/F, XylAc/F/XylAc	1340
23/24/25	GluAc/XylAc/F, GluAc/F/XylAc, F/GluAc/XylAc	1412
26/27	XylAc/XylAc/SPy, XylAc/SPy/XylAc	1431
28/29	GluAc/GluAc/F, GluAc/F/GluAc	1484
30/31/32	GluAc/XylAc/SPy, GluAc/SPy/XylAc, XylAc/GluAc/SPy	1503
33/34	GluAc/GluAc/SPy, GluAc/SPy/GluAc	1575
35	XylAc/XylAc/XylAc	1612
36/37	GluAc/XylAc/XylAc, XylAc/GluAc/XylAc	1684
38/39	GluAc/GluAc/XylAc, GluAc/XylAc/GluAc	1756
40	GluAc/GluAc/GluAc	1828

The highlighted compounds were found in the MS analysis, thus indicating that 17 members of the target 18-member library were synthesized and the SPy moiety is less reactive than the thiosugars.

Cell Binding Assays

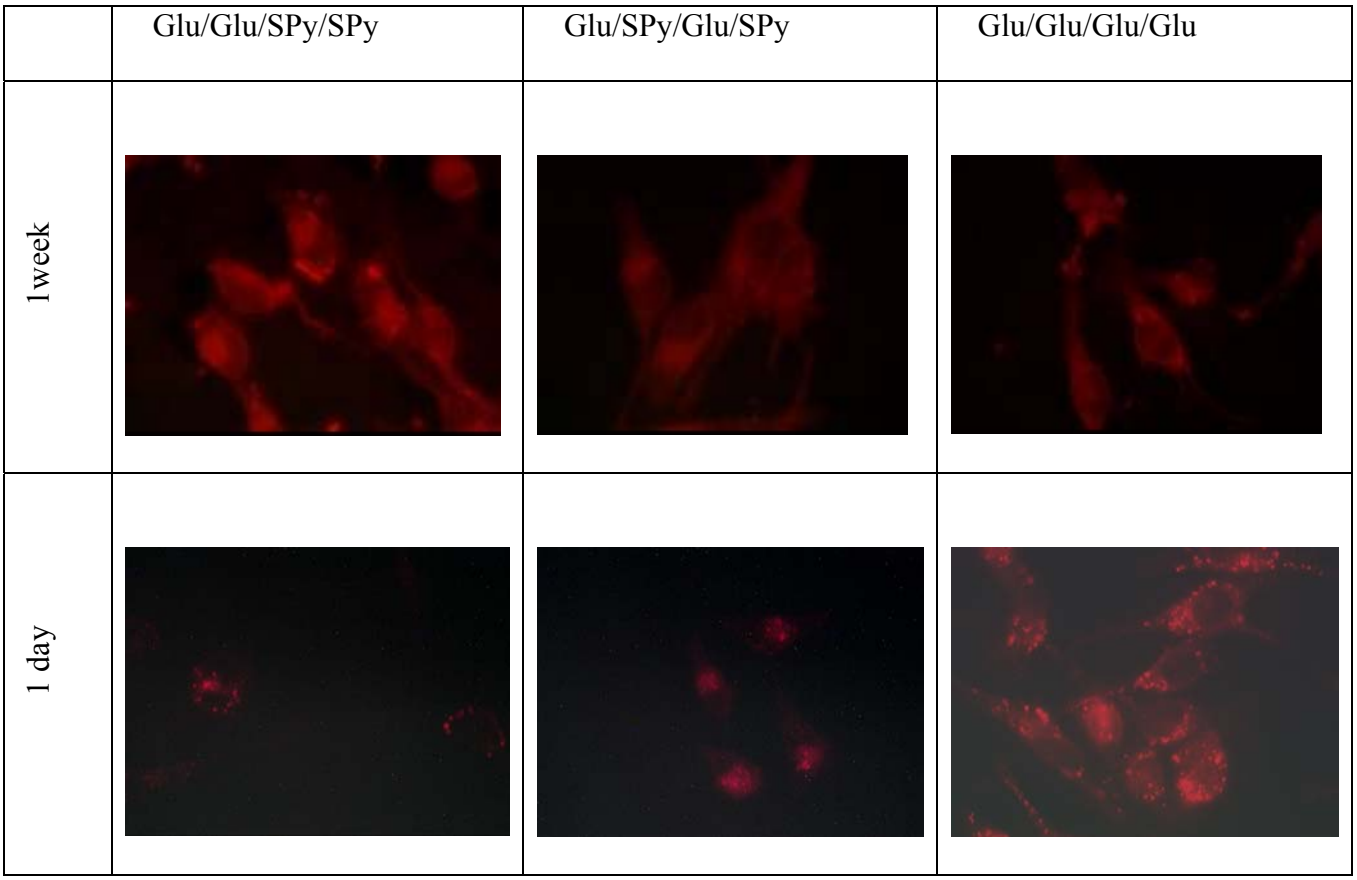


Figure ESI-18. Different affinities of winning Glu_2SPy_2 isomers toward human breast cancer MDA-MB-231 cells assayed by fluorescence images and compared with the Glu/Glu/Glu/Glu porphyrin (10 μM incubated with cells followed by rinsing and fixing the cells). Magnification = 60X.

Experimental

FLim program:

This Java-based program is for handling (FL)uorescence (im)ages of cells that have been tagged with some kind of fluorescence probe. It allows for the relative fluorescence intensity between images to be quickly compared. The program opens images in jpg, png, or gif format, and only saves in jpg format. One of the basic functions that it performs is background subtraction. This is performed by selecting a rectangular region, then pressing "BG Color" to set it, followed by “Run” to execute that function.

Relative intensities are computed using a pixel sampling method, in which the weighted average of the most intense pixels (based on the red, green, or blue value) within a specific range. If no errors occurred during the calculation process, then the error label displays "none", however, if it says "under sampled" then not enough pixels were sampled. This can be solved by either reducing the

pixels to sample, or adjusting the range. The distribution of pixels can also be evaluated. A good distribution is one in which the minimum intensity is greater than the lower limit of the range, and the maximum is less than the upper limit of the range. The distribution of intensities also shows which image has the most intense fluorescence. When comparing images, it is important that the same range of parameters including the number of pixels sampled be used for all images. Another important point to make is that the program scans an entire image, rather than looks at a selected section/region of that image. By doing this, it gives a more accurate intensity calculation.

Uptake of amphipathic uncharged porphyrins: isomers and aggregation

Cells cultured on glass cover slips, using the same conditions reported previously, were incubated with 10 μM of the three porphyrin derivatives under identical conditions. After rinsing the unbound compounds from the cells on the cover slips and fixing the cells, fluorescence images of the cells were taken on the same day of fixing and one week later. The observed fluorescence intensity was taken to be proportional to the quantity of porphyrin bound to the cells, and was quantified by comparing the integrated RGB vectors for identical areas (see experimental procedures). When cells are treated with the uncharged 5,10-isomer (Glu/Glu/Py/Py) or the 5,-15-isomer (Glu/Py/Glu/Py) for 24 hours, rinsed, and fixed, little fluorescence is observed by fluorescence microscopy just after fixing the cells compared to the bright luminescence of cells treated with Glu/Glu/Glu/Glu. However, when the same slides bearing the cells are re-examined one week later, the fluorescence micrographs show a large increase in luminescence (Figure ESI-18). Since the cells were rinsed to remove unbound porphyrins, no further uptake of porphyrin is possible. Thus the images in Figure ESI-18 clearly show that the affinity of Glu/Glu/SPy/SPy to the cancer cells is 2-3 fold greater than the affinity of Glu/SPy/Glu/SPy.

These results suggest that Glu/Glu/SPy/SPy and Glu/SPy/Glu/SPy bind and/or enter the cells as nanoscaled aggregates, which have significantly quenched fluorescence. The UV-VIS spectra of both isomers in polar organic solvents (e.g. 1:1 CH_3OH/DME, Figure ESI-19, DME is ethylene glycol dimethyl ether) are typical of porphyrin derivatives based on $TPPF_{20}$. The Soret bands of the electronic spectra of both compounds in the DMEM cell culture media (without phenol red) are significantly broadened and split, which is typical of aggregated porphyrins. Dynamic light scattering (DLS) of freshly prepared 10 μM aqueous solutions of Glu/Glu/SPy/SPy and Glu/SPy/Glu/SPy indicates the average particle diameters are 30 nm and 50 nm respectively, but the dispersities are large. The absorption of nanoparticles by cells has been well documented.[2-11] Thus it is reasonable to hypothesize that nanoparticles/aggregates of Glu/Glu/SPy/SPy or Glu/SPy/Glu/SPy are formed in the cell culture medium wherein their fluorescence is quenched by well-understood mechanisms.[12-14,15] Once absorbed by the cells, the nanoparticles slowly deaggregate due to interactions with various cellular components, which are manifested by the observed increase in fluorescence intensity (compare 1 day to 1 week in Figure ESI-18). The mechanism of nanoparticle uptake was not specifically evaluated, but may involve endocytosis and/or binding to cell membranes and nanoparticles reorganization. Also the cells may take up smaller nanoparticles preferentially.

The working model for the difference in uptake is that Glu/Glu/SPy/SPy is polar and has a hydrophilic side and a hydrophobic side, thus partitions into the cell membrane better than compound Glu/SPy/Glu/SPy, which is consistent with previous studies comparing these types of isomers.[16] The hierarchical organization and stability of porphyrinic nanoparticles are known to be highly dependent on the chemical structure.[17, 18]

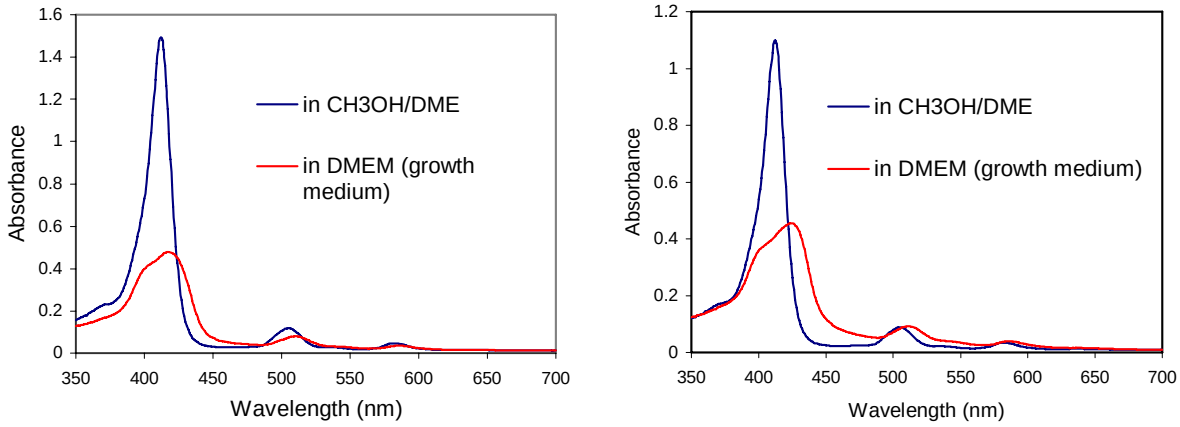
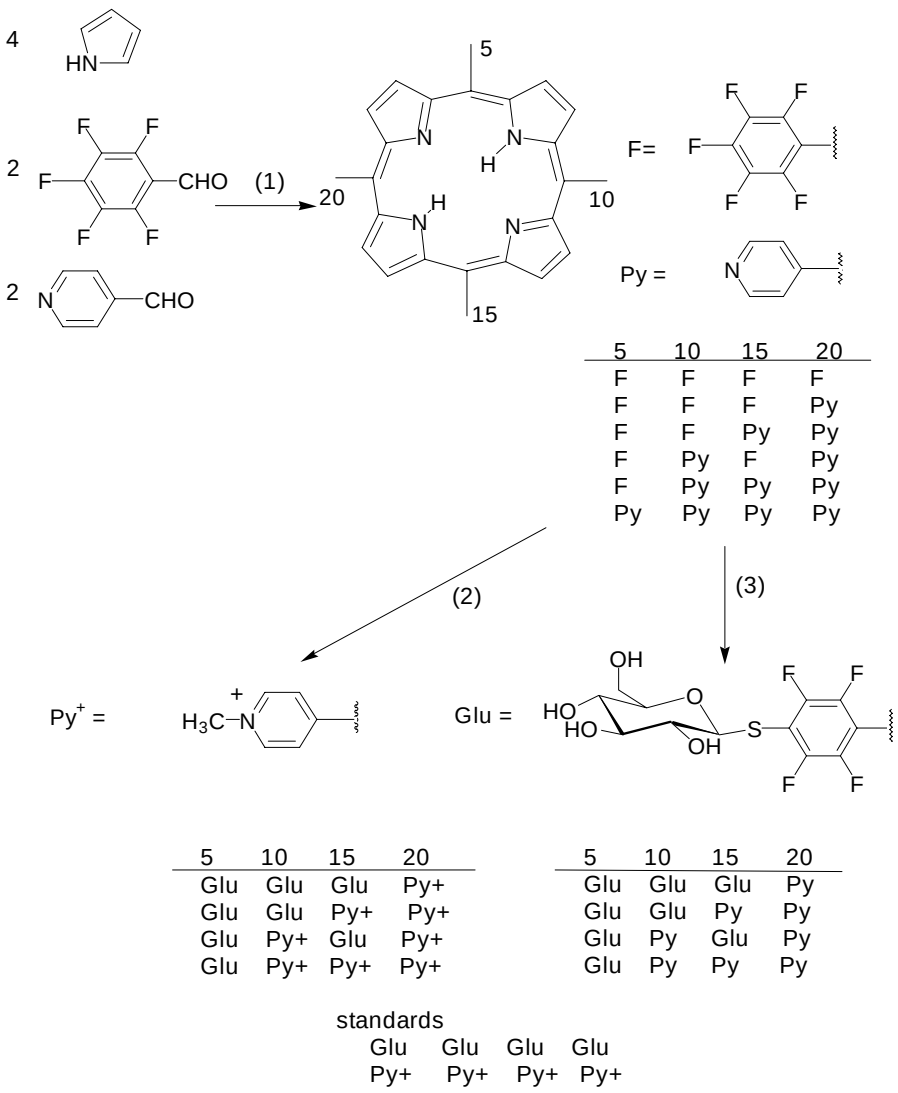


Figure ESI-19. The UV-VIS spectra of (A) Glu/Glu/SPy/SPy and (B) Glu/SPy/Glu/SPy in an organic solvent mixture of CH_3OH/DME (1:1 v/v) and aqueous growth medium DMEM without phenol red. The broadened and red-shifted Soret bands are indicative of aggregation.

Derivatives with the pyridyl and pyridinium directly attached to the porphyrin



5	10	15	20
F	F	F	F
F	F	F	Py
F	F	Py	Py
F	Py	F	Py
F	Py	Py	Py
Py	Py	Py	Py

5	10	15	20
Glu	Glu	Glu	Py+
Glu	Glu	Py+	Py+
Glu	Py+	Glu	Py+
Glu	Py+	Py+	Py+

5	10	15	20
Glu	Glu	Glu	Py
Glu	Glu	Py	Py
Glu	Py	Glu	Py
Glu	Py	Py	Py

standards

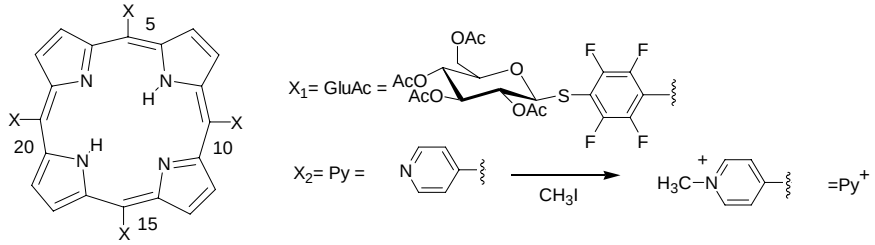
Glu	Glu	Glu	Glu
Py+	Py+	Py+	Py+

Scheme ESI-4: Top: general reaction scheme for a typical mixed aryl aldehyde porphyrin synthesis (1) uses a 2:1:1 ratio of pyrrole: pyridinecarboxaldehyde: pentafluorobenzaldehyde in refluxing propionic acid, which yields six isomers.[1] After chromatographic separation of the desired compounds, (2) the formation of the N-methyl pyridinium salt uses an excess of CH_3I in CH_2Cl_2 and, (3) the substitution of the 4-fluoro group uses the protected thioglucose in $CH_3OH/DMF/CHCl_3$ at room temperature with diethylamine followed by deprotection with four equivalents of $NaOCH_3$ in CH_3OH/CH_2Cl_2

The reactivity of the pentafluorophenyl group is similar to the parent $TPPF_{20}$. For example, the protected thioglucose is readily appended to 5,10-di-(pentafluorophenyl)-15,20-di-(pyridin-4-

yl)porphyrin (F/F/Py/Py); and 5,15-di-(pentafluorophenyl)-10,20-di-(pyridin-4-yl)porphyrin (F/Py/F/Py), using 4 equivalents of the thioglucose in a 4:4:1 (v/v) mixture of DMF/chloroform/methanol as the solvent, while stirring at RT under N_2 for one day to yield the sugar appended porphyrin with more than 80% isolated yields. The quaternisation of the pyridyl functions of the porphyrins were carried out by reaction with CH_3I followed by anion exchange by Cl^- using Amberlite resin. Deprotection of the protected thioglucose was then carried out as usual with stoichiometric amount $NaOCH_3$.

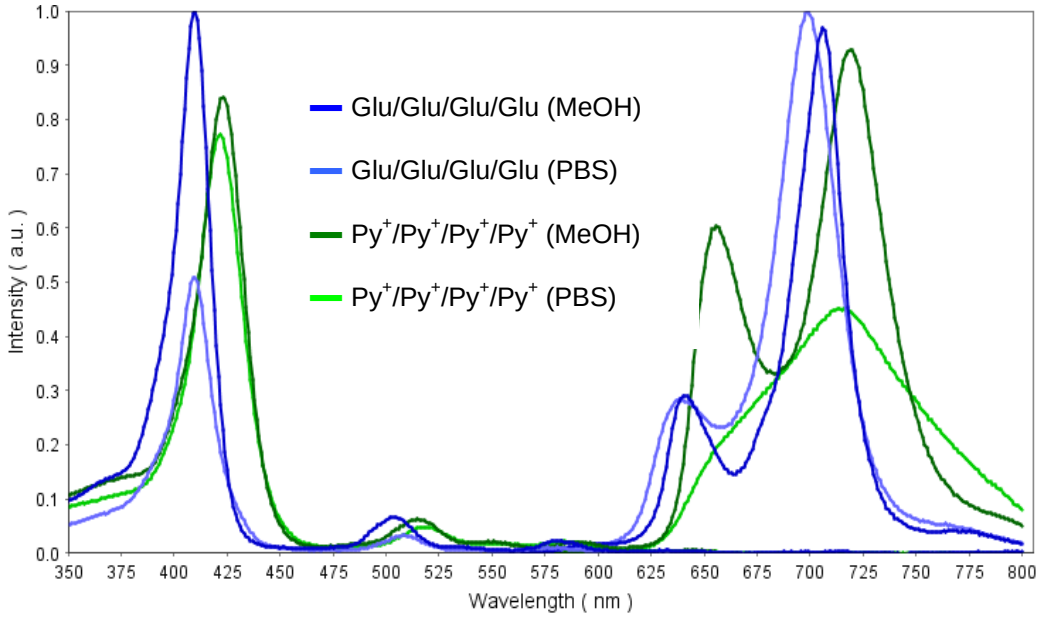
Table ESI-5. Yields of substitution reactions on mixed aryl pentafluorophenyl, pyridyl porphyrins[a].



Porphyrin Product				Thio reagent	Solvent	Rxn. time	Yield (%)
5	10	15	20				
Py	Py	GluAc	GluAc	2,3,4,6-tetra-O-acetyl-glucosylthioacetate	DMF:$CHCl_3$:CH_3OH (4:4:1)	1 day	82
Py	GluAc	Py	GluAc	2,3,4,6-tetra-O-acetyl-glucosylthioacetate	DMF:$CHCl_3$:CH_3OH (4:4:1)	1 day	84
Py	GluAc	GluAc	GluAc	2,3,4,6-tetra-O-acetyl-glucosylthioacetate	DMF:$CHCl_3$:CH_3OH (4:4:1)	1 day	83
Py	Py	Py	GluAc	2,3,4,6-tetra-O-acetyl-glucosylthioacetate	DMF:$CHCl_3$:CH_3OH (4:4:1)	1 day	90

[a]Reactions are run under an inert atmosphere, 20 equivalents DEA, magnetic stirring

Optical properties



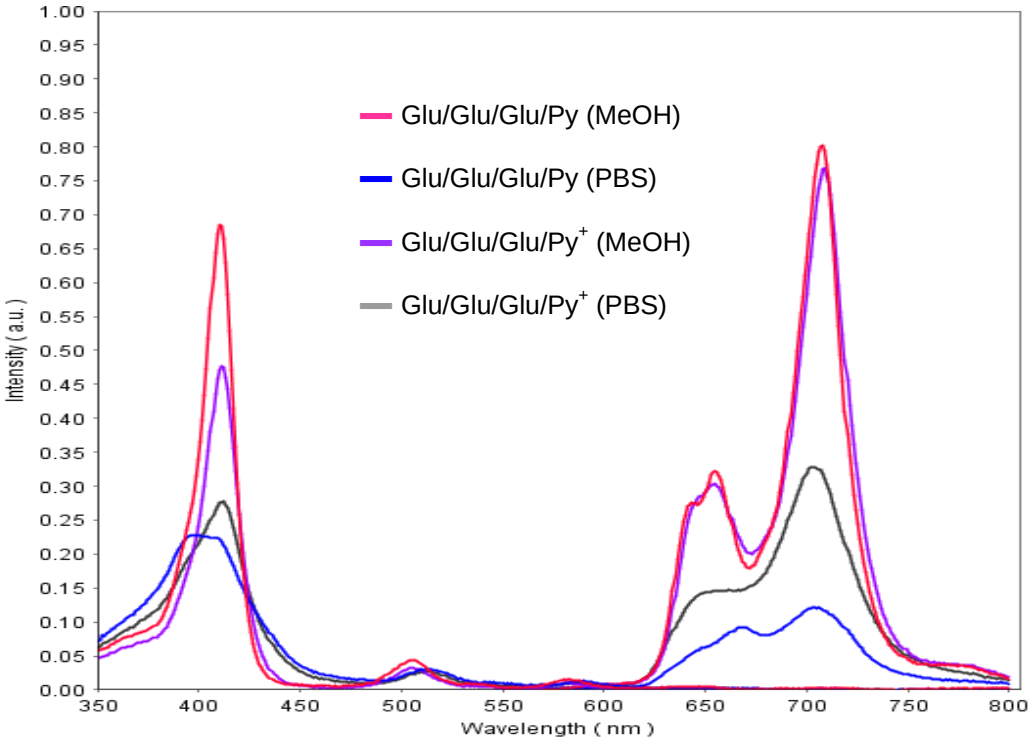


Figure ESI-20: Overlay plots of absorption (left) and emission (right) spectra for the mixed aryl pyridyl porphyrins (structures in Scheme ESI-4), ca. 2.5 μM in methanol and aqueous PBS cell culture media.

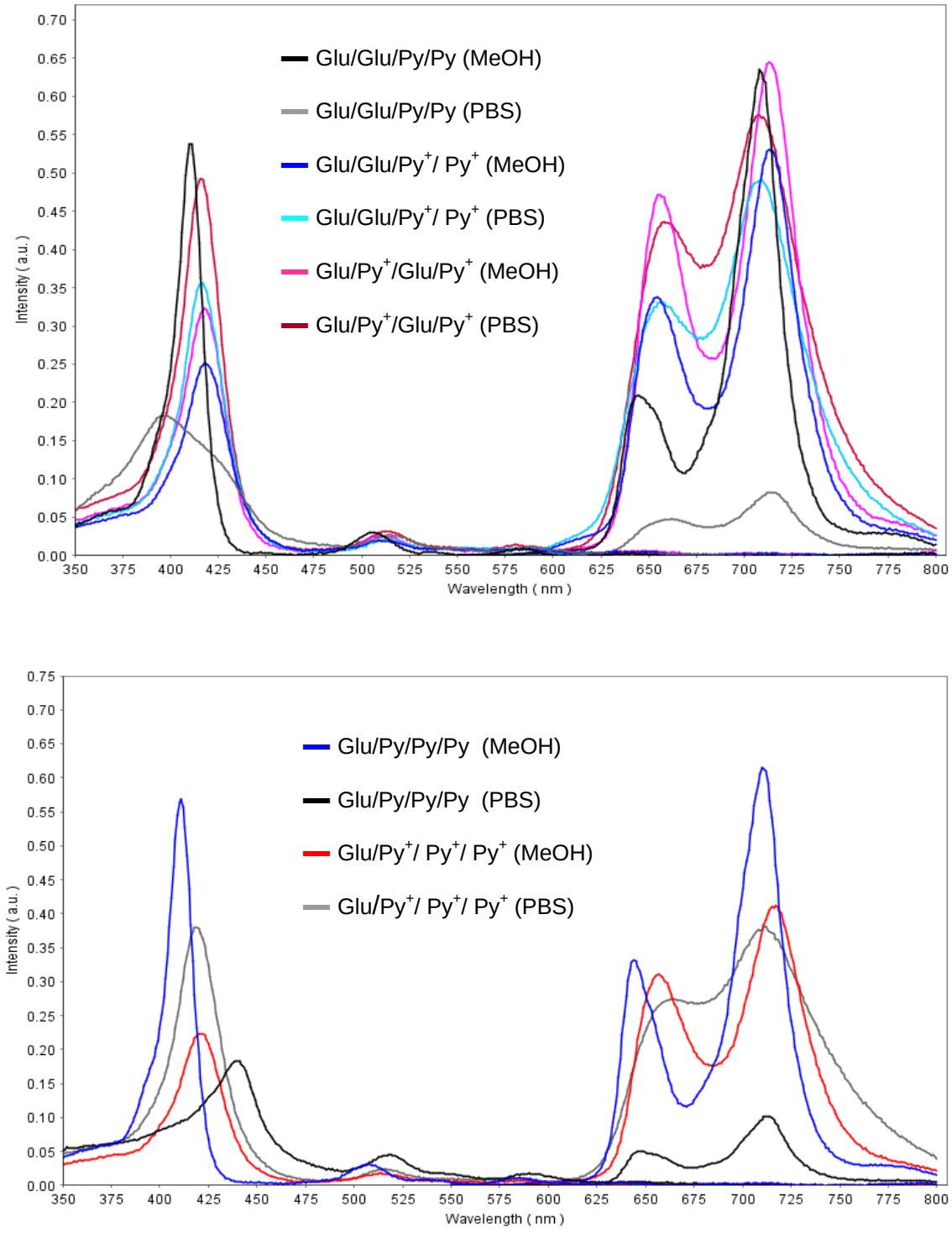


Figure ESI-21: Overlay plots of absorption (left) and emission (right) spectra for the mixed aryl pyridyl porphyrins (structures in Scheme ESI-4), ca. 2.5 µM in methanol and aqueous PBS cell culture media.

The triplet quantum yield for TPP is 80% ± 10%, and for $TPPF_{20}$ is >80%.[19] The fluorescence quantum yields of these mixed aryl derivatives in methanol and PBS is shown in Table ESI-6. Because these are measured indirectly using a known standard compound, it should be noted that these values may have some systematic error; however all experiments were performed on the same day and using identical concentrations to minimize any experimental errors.

Quantum Yield Calculations

From the normalized absorption and corrected emission spectra, the quantum yield for radiative decay can be indirectly obtained using the following equation from George et al.[20] In this equation, Q is the quantum yield of the unknown sample; Q_R is the quantum yield (Φ_F) of the standard sample, I_R and I are the integrated intensity for the standard and unknown samples, respectively. OD represents the optical density and η is the refractive index of the solvent used. The standard or reference sample used for the quantum yield determination was cresyl violet (Φ_F = 0.54, spectral range 600 – 650 nm) dissolved in methanol.[21, 22]

$$Q = Q_R \frac{I}{I_R} \frac{OD_R}{OD} \frac{n^2}{n_R^2}$$

	Quantum Yield	
	MeOH	PBS
Cresyl Violet	54%	
Glu/Glu/Glu/Glu	7%	7%
Py/Glu/Glu/Glu	9%	3%
Py/Py/Glu/ Glu	9%	3%
Py/Py/Py/Glu	9%	3%
Py^+/Glu/Glu/Glu	10%	7%
Py^+/Py^+/Glu/Glu	10%	8%
Py^+/Glu/Py^+/Glu	10%	7%
Py^+/Py^+/Py^+/Glu	10%	7%
Py^+/Py^+/Py^+/Py^+	6%	4%

Table ESI-6. Fluorescence quantum yield (Φ_F) determinations for the mixed aryl porphyrins 2.5 μM in methanol and aqueous PBS media.

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